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⑰ **Phenothiazone derivatives and analogs.**

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March 1970, page 406, no. 66965m, Columbus,
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Description

BACKGROUND OF THE INVENTION

This invention involves certain phenothiazone derivatives and analogs. These compounds are useful as inhibitors of mammalian leukotriene biosynthesis. As such, these compounds are useful therapeutic agents for treating allergic conditions, asthma, cardiovascular disorders and inflammation.

The leukotrienes are a novel group of biologically active mediators derived from arachidonic acid through the action of lipoxygenase enzyme systems. There are two groups of leukotrienes derived from the common unstable precursor Leukotriene A₄. The first of these are the peptido-lipid leukotrienes, the most important being Leukotrienes C₄ and D₄. These compounds collectively account for the biologically active material known as the slow reacting substance of anaphylaxis.

The leukotrienes are potent smooth muscle contracting agents, particularly on respiratory smooth muscle but also on other tissues (e.g. gall bladder). In addition, they promote mucous production, modulate vascular permeability changes and are potent inflammatory agents in human skin. The most important compound in the second group of leukotrienes is Leukotriene B₄, a dihydroxy fatty acid. This compound is a potent chemotactic agent for neutrophils and eosinophils and in addition, may modulate a number of other functions of these cells. It also effects other cell types such as lymphocytes and for example may modulate the action of T-suppressor cells and natural killer cells. When injected *in vivo*, in addition to promoting the accumulation of leukocytes, Leukotriene B₄ is also a potent hyperalgesic agent and can modulate vascular permeability changes through a neutrophil dependent mechanism. Both groups of leukotrienes are formed following oxygenation of arachidonic acid through the action of a 5-lipoxygenase enzyme. See for example, D. M. Bailey *et al.*, *Ann. Rpts. Med. Chem.* 17 203 (1982).

Respiratory Conditions

a) *Asthma*. The leukotrienes are potent spasmogens of human trachea, bronchus and lung parenchymal strips, and when administered to normal volunteers as aerosols are 3,800 times more potent than histamine at inducing a 50% decrease in air flow at 30% of vital capacity. They mediate increases in vascular permeability in animals and promote mucous production in human bronchial explants. In addition, Leukotriene B₄ may also mediate mucous production and could be an important mediator of neutrophil and eosinophil accumulation in asthmatic lungs. 5-Lipoxygenase products are also thought to be regulators of mast cell degranulation and recent studies with human lung mast cells have suggested that 5-Lipoxygenase inhibitors, but not corticosteroids, may suppress antigen-induced mast cell degranulation. *In vitro* studies have shown that antigen challenge of human lung results in the release of leukotrienes and in addition purified human mast cells can produce substantial amounts of leukotrienes. There is therefore good evidence that the leukotrienes are important mediators of human asthma. 5-Lipoxygenase inhibitors would therefore be a new class of drugs for the treatment of asthma. See for example, B. Samuelsson, *Science* 220 568—575 (1983).

Skin Diseases

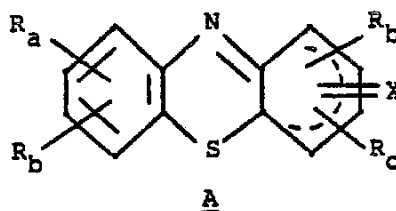
a) *Psoriasis*. Psoriasis is a human skin disease which effects between two and six percent of the population. There is no adequate therapy for psoriasis and related skin conditions. The evidence for leukotriene involvement in these diseases is as follows. One of the earliest events in the development of prepapillary lesions is the recruitment of leukocytes to the skin site. Injection of Leukotriene B₄ into human skin results in a pronounced neutrophil accumulation. There are gross abnormalities in arachidonic acid metabolism in human psoriatic skin. In particular, highly elevated levels of free arachidonic acid can be measured as well as large amounts of lipoxygenase products. Leukotriene B₄ has been detected in psoriatic lesions, but not in uninvolved skin, in biologically significant amounts.

Allergic Conditions

a) Leukotrienes can be measured in nasal washings from patients with allergic rhinitis and are greatly elevated following antigen challenge. Leukotrienes may mediate this disease through their ability to regulate mast cell degranulation, by modulating mucous production and mucociliary clearance and by mediating the accumulation of inflammatory leukocytes.

Leukotrienes can also mediate other diseases. These include atopic dermatitis, gouty arthritis and gall bladder spasms. In addition, they may have a role in cardiovascular disease because leukotrienes C₄ and D₄ act as coronary and cerebral arterial vasoconstrictors and these compounds may also have negative inotropic effects on the myocardium. In addition, the leukotrienes are important mediators of inflammatory diseases through their ability to modulate leukocyte and lymphocyte function.

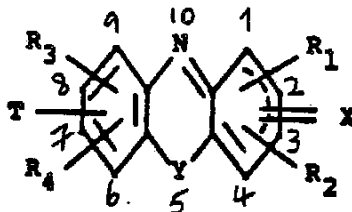
A number of Phenothiazone derivatives of the general Formula:



especially when X is O are taught in the literature; see for example Terdic *et al.*, *Rev. Roum. Chim.* 13, 833—8 (1968); Beckett *et al.*, *Xenobiotica* 8, 721—36 (1978); Panea *et al.*, *Rev. Roum. Chim.* 25, 691—5 (1980); Bhargava *et al.*, *Gazz. Chim. Ital.* 110, 201—3 (1980); Bodea *et al.*, *Ann. Chem.* 698, 186—90, (1966); Sugita *et al.*, *Nippon Kagaku Zasshi* 89, 309—15 (1968); Broser *et al.*, *Rev. Roum. Chim.* 17, 1747—53 (1972); Bodea *et al.*, *Ann. Chem.* 715, 122—7 (1968); Bodea *et al.*, *Rev. Roum. Chim.* 13, 971—6 1241—4 (1968); Sugita *et al.*, Japanese Patent No. 73, 22,714 (1973); Tsyino, *Tet. Lett.* (10), 763—6 (1969); Rosebourn *et al.*, *J. Pharm. Sci.* 66, 1395—8 (1977); Shakii *et al.*, *Yakugaku Zasshi* 86, 541—3 (1966); Bodea *et al.*, *Ann. Chem.* 614, 171—6 (1958); Collier *et al.*, *Can. J. Med. Sci.* 31, 195—201 (1953); and Collier *et al.*, *Can. J. Med. Sci.* 30, 443—6 (1952). However, none of the compounds of Formula A is taught to have mammalian leukotriene biosynthesis inhibitor activity.

It has been discovered that compounds of Formula A and especially those where X is O are effective inhibitors of mammalian leukotriene biosynthesis and are thus useful therapeutic agents for treating conditions such as asthma, allergies, inflammation and certain skin diseases in humans.

This invention provides the use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of the Formula I, a compound that is a salt of a compound of the Formula I, or a pharmaceutical composition containing such a compound:



in which

X is in the 1 or 3 position and is O, S or NR;
R is H, C₁₋₆ branched or linear alkyl, CN or phenyl;
Y is O, Se, S, SO, SO₂ or NR; and the broken line represents a double bond between the 1 and 2 or 2 and 3 positions;

each of R₁, R₂, R₃ and R₄ independently of the others, is

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) C₂₋₆ alkenyl,
- (4) —(CH₂)_n M

where n is 0 or an integer from 1 to 6 and M is

- (a) OR₅,
- (b) halogen,
- (c) CF₃,
- (d) SR₅ where R₅ is H; C₁₋₆ alkyl; benzyl; phenyl or substituted phenyl where the substituents are C₁₋₃ alkyl, halogen, CN, CF₃, COOR₆, CH₂COOR₆, (CH₂)_nNR₈R₉ where n is 0, 1 or 2, C₁₋₃ alkoxy, OH or C₁₋₆ haloalkyl; —(CH₂)_mCOOR₆, where m is 0 or an integer from 1 to 6 and R₆ is H, phenyl or C₁₋₆ alkyl; CN, formyl, CF₃ or CH₂—R₁₂, where R₁₂ is C₁₋₅ alkyl, phenyl or dimethylamino;
- (e) phenyl or substituted phenyl as defined above for R₅;
- (f) COOR₆;

(g)

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{R}_{14} \end{array}$$

where R₁₄ is H, (CH₂)_n COOR₆ where n is 0 or an integer from 1 to 4, C₁₋₆ alkyl, CF₃, phenyl, or substituted phenyl as defined above for R₅;

(h) tetrazole;

(i)

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{—NH—C—R}_7 \end{array}$$

where R₇ is C₁₋₆ alkyl, benzyl or phenyl;

(j) $-\text{NR}_8\text{R}_9$ where R_8 and R_9 are independently selected from H, phenyl or substituted phenyl as defined above for R_5 or C_{1-4} alkyl, C_{1-4} alkylaminoalkyl, or may be joined through the N to form a 4-methyl piperazinyl radical;

5 (k) $-\text{NHSO}_2\text{R}_{10}$ where R_{10} is OH, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl or CF_3 ;



10 (m) $-\text{SOR}_{11}$ where R_{11} is C_{1-6} alkyl, phenyl or substituted phenyl as defined above for R_5 , $(\text{CH}_2)_m\text{COOR}_6$ where m is 1 to 6, CN, formyl or CF_3 ;

(n) $-\text{CONR}_8\text{R}_9$;

(o) $-\text{SO}_2\text{NR}_8\text{R}_9$;

15 (p) $-\text{SO}_2\text{R}_{13}$ where R_{13} is OH, H, C_{1-6} alkyl, phenyl or substituted phenyl as defined above for R_5 , $(\text{CH}_2)_m\text{COOR}_6$ where m is 1 to 6, CN or CF_3 ;

(q) NO_2 ;



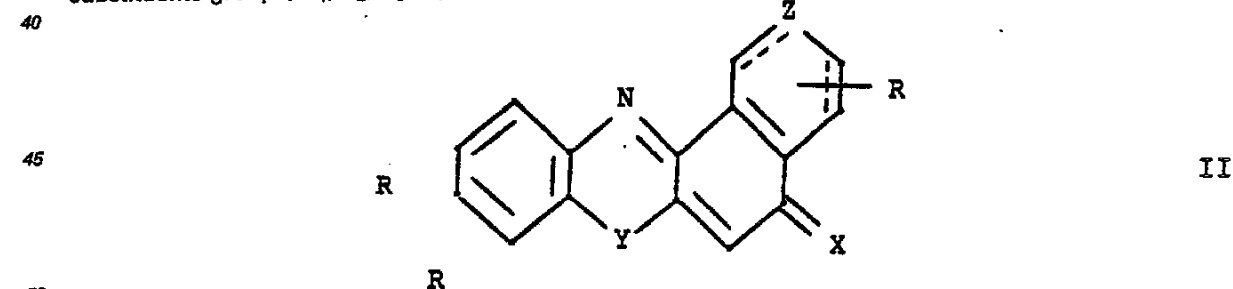
30 (u) $-\text{CN}$; or

(v) $\text{NR}_{15}\text{R}_{16}$ where R_{15} and R_{16} are such that $\text{HNR}_{15}\text{R}_{16}$ is an essential amino acid;

or any two of R_1 , R_2 , R_3 and R_4 are joined to form a fourth saturated or unsaturated C_{5-6} ring; and T is H, halogen or CF_3 .

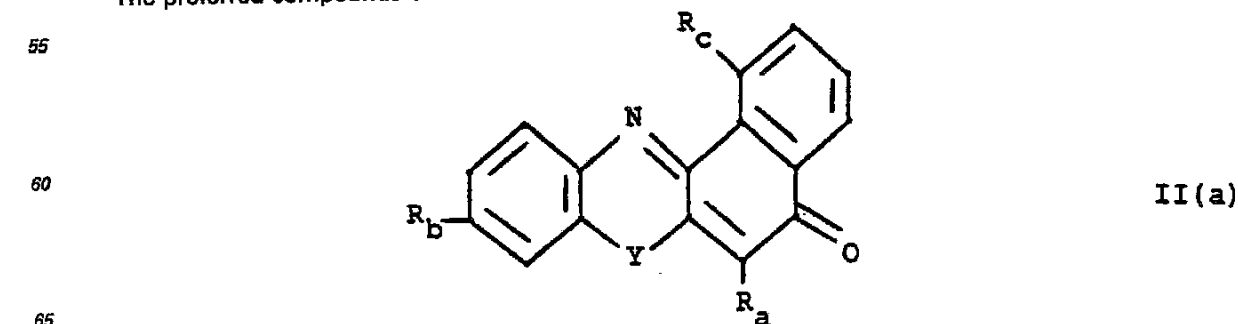
Certain compounds of Formula (I) are novel and constitute another embodiment of the invention.

35 The numbers surrounding Formula I designate the substituent positions. T, R_1 , R_2 , R_3 and R_4 may be positioned anywhere in the structure. R_1 , R_2 , R_3 and R_4 may also be joined, e.g. as $-(\text{CH}_2)_{3-4}-$, to add a fourth ring to the basic three ring structure. This fourth ring may have five or six carbon atoms and may be saturated or unsaturated. For example, compounds of Formula II may be prepared by linking two of the substituents groups; R_1 , R_2 , R_3 , R_4 :



50 wherein Z may be CH, CH_2 or a bond, the broken lines represent optional double bonds and R represents the substituent groups of Formula I (R_1 , R_2 , R_3 , R_4 and/or T) not used to create the fourth ring.

The preferred compounds of Formula II have the structure II(a):



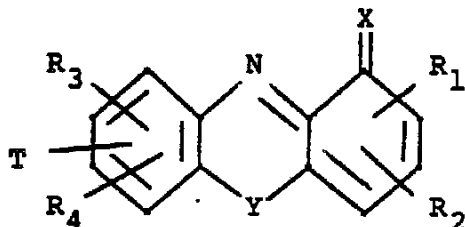
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wherein R_a is selected from hydrogen, halogen (F, Br, Cl, I), CH_3 , CF_3 , COR_d , NHR_d , SR_d and OR_d ; R_b is selected from hydrogen, halogen (F, Br, Cl, I), CH_3 , CF_3 , CH_2OH , OR_d , SR_d , COR_d , $COOR_d$, CH_2COOR_d and $CH(CH_3)COOR_d$; R_d is hydrogen, phenyl, C_{1-4} straight or branched alkyl; R_c is selected from hydrogen or OR_d ; and Y is selected from O, S, SO or SO_2 .

5 Where possible, appropriate pharmaceutically acceptable salts of Formula I are included e.g., carboxylic or mineral acid addition salts where Formula I is basic and metal salts e.g. Na, K, NH_4 where Formula I is acidic.

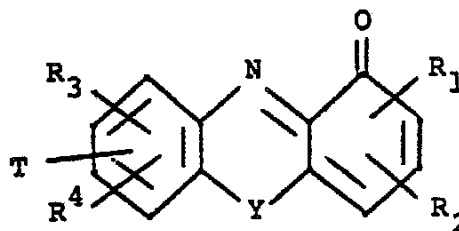
The term alkyl, unless indicated otherwise, indicates straight chain, branched chain and cycloalkyl groups. The term halogen or halo, unless otherwise indicated, includes Cl, Br, I and F.

10 A group of preferred compositions contain a compound of the Formula:



I (a)

20 More preferred Formula I(a) compounds are those wherein X is O or NH and Y is S, O, SO or SO_2 . Still more preferred I(a) compounds are those having the Formula:



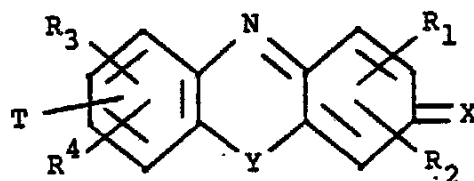
I (a)

wherein:

- a) T, R_3 and R_2 are hydrogens,
- b) T, R_1 , R_2 are hydrogens,
- c) T, R_3 and R_4 are hydrogens,
- d) T, R_1 , R_2 , R_3 are hydrogens or
- e) T, R_3 , R_4 , R_2 are hydrogens.

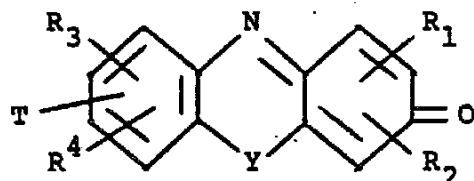
wherein R_1 , R_2 , R_3 , R_4 and T are as defined for Formula I.

Another group of preferred compositions contain compounds of the Formula I(b):



I (b)

More preferred compounds of Formula I(b) are those having the Formula wherein X is O or NH and Y is O, S, SO, SO_2 . Still more preferred compounds of Formula I(b) are those of the formula I(c):



I (c)

wherein:

- a) T, R_3 and R_2 are hydrogens,
- b) T, R_1 , R_2 are hydrogens,
- c) T, R_3 and R_4 are hydrogens,
- d) T, R_1 , R_2 , R_3 are hydrogens,

- e) T, R₃, R₄, R₂ are hydrogens,
 f) T, R₃ and R₄ are hydrogens and R₁ is in position 4,
 g) T, R₃, R₂ are hydrogens and R₁ is in position 4,
 h) T, R₄, R₃, R₂ are hydrogens and R₁ is in position 4,
 5 i) R₂ and R₃ are hydrogens,
 j) R₁ and R₂ are hydrogens,
 k) R₃ and R₄ are hydrogens,
 l) R₂, R₃ are hydrogens and T is in position 4,
 m) T and R₃ are hydrogens and R₂ is in position 4,
 10 n) T and R₃ are hydrogens and R₁ is in position 4 and R₂ is in position 2,
 o) T and R₃ are hydrogens and R₄ is in position 7, R₂ is in position 4 and R₁ is in position 2.
 (p) T is hydrogen, R₁, R₂, R₃, and R₄ are in positions 1, 2, 4 and 7, respectively.
 A particularly preferred series of Formula I(c) compounds are those in which n = 0 or 1 in the unit
 (CH₂)_nM.
 15 Examples of Formula I compounds useful in the present compositions are tabulated below. In each of
 the tables the numbers preceding the T and the R₁—R₄ definitions indicate the substituent position in the
 structure.

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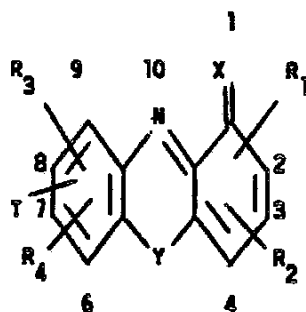
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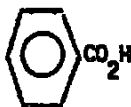
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TABLE 1

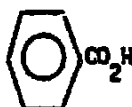
Compounds of the Formula



Number	Y	X	R ₁	R ₂	R ₃	R ₄	T
1	O	O	2-t-Bu	8-t-Bu	4-t-Bu	6-t-Bu	H
2	O	O	2-t-Bu	H	4-Me	H	H
3	N-CH ₃ , S, O, Se, SO or SO ₂	O	2-Cl	H	H	H	H
4	"	O	2-SCF ₃	H	H	H	
5	"	O	2-S 	H	H	H	H
6	"	O	2-CN	H	H	H	H
7	"	O	H	3-CO ₂ Et	H	H	H
8	"	O	H	3-Cl	H	H	H
9	"	O	H	H	4-Cl	H	H
10	"	O	H	H	4-SO ₂ CH ₃	H	H
11	"	O	2-Cl	H	4-Cl	H	H
12	"	NH	2-Cl	H	4-Cl	H	H
13	"	NH	H	H	H	H	H
14	N-CN	O	2-Cl	H	4-Cl	H	H
15	S	O	H	H	H	H	H
16	S	O	2-Cl	3-Cl	4-Cl	7-Cl	9-Cl
17	S	O	2-Br	3-Br	4-Br	7-Br	9-Br
18	S	O	H	H	H	7-SO ₂ CH ₃	H
19	S	O	2-Cl	H	4-SO ₂ CH ₃	H	H
20	S	O	2-F	H	4-Cl	H	H
21	S	O	2-Br	H	H	H	H

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TABLE 1 continued

Number	Y	X	R ₁	R ₂	R ₃	R ₄	T
22	S	O	2-CF ₃	H	H	H	H
23	S	O	2-SCF ₃	H	H	H	H
24	S	O	2-SO ₂ CF ₃	H	H	H	H
25	S	O	H	3-Cl	H	H	H
26	S	O	H	3-CO ₂ Et	H	H	H
27	S	O	H	3-CO ₂ H	H	H	H
28	S	O	H	3-CN	H	H	H
29	S	O	H	3-SCF ₃	H	H	H
30	S	O	H	H	4-Cl	H	H
31	S	O	H	H	4-SCF ₃	H	H
32	S	O	H	H	4-Cl	H	H
33	S	O	2-Br	H	4-Br	H	H
34	S	O	2-Cl	H	H	8-CN	H
35	S	O	2-Cl	H	H	8-CO ₂ Et	H
36	S	O	2-Cl	H	H	8-CO ₂ H	H
37	S	O	2-Cl	H	H	8-CF ₃	H
38	S	O	2-Cl	H	H	7-SO ₂ CH ₃	H
39	S	O	H	3-CONMe ₂	H	H	H
40	S	O	2-Cl	H	H	7-OCH ₃	H
41	S	O	2-S 	H	H	H	H
42	S	O	2-SO ₂ CH ₃	H	H	H	H
43	S	O	2-CH ₂ CH=CH ₂	H	4-CH ₂ CH=CH ₂	H	H
44	S	O	H	3-N(CH ₃) ₂	H	H	H
45	S	O	H	H	4-Cl	7-S-C ₆ H ₅	H
46	S	O	2-CH ₂ CO ₂ H	H	H	H	H
47	S	O	2-Cl	H	4-SCH ₂ CO ₂ H	H	H
48	S	O	2-COCH ₃	H	H	7-OCH ₃	H
49	S	O	H	H	4-CO-C ₆ H ₅	7-OCH ₃	H
50	S	NH	2-Cl	H	4-Cl	H	H

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TABLE 1 continued

Number	Y	X	R ₁	R ₂	R ₃	R ₄	T
51	S	NH	H	3-N(CH ₃) ₂	H	H	H
52	S	NH	2-SCH ₃	H	4-SCH ₃	H	H
53	S	O	H	H	H	H	H
54	S	NH	H	H	H	H	H
55	S	NH.HCl	H	H	H	H	H
56	S	O	H	H	H	H	H
57	O	O	H	H	H	H	H
58	O	NH	H	H	H	H	H
59	O	S	H	H	H	H	H
60	O	NH.HCl	H	H	H	H	H
61	Se	O	H	H	H	H	H
62	Se	NH	H	H	H	H	H
63	Se	S	H	H	H	H	H
64	NH	NH.HCl	H	H	H	H	H
65	NH	S	H	H	H	H	H
66	O	O	4-Cl	H	H	H	H
67	O	O	4-Cl	H	7-OMe	H	H
68	O	O	4-Me	H	H	H	H
69	O	O	H	2-Cl	H	H	H
70	O	O	4-Cl	2-S-pPAA*	H	H	H
71	Se	O	4-Cl	H	H	H	H
72	Se	O	4-Cl	H	7-OMe	H	H
73	Se	O	4-Me	H	H	H	H
74	Se	O	4-Cl	2-S-pPAA*	H	H	H
75	N-CH ₃	O	4-Cl	H	H	H	H
76	N-C ₆ H ₅	O	4-Cl	H	7-OMe	H	H
77	N-H	O	4-Cl	2-S-pPAA*	H	H	H
78	S	O	4-Cl	H	H	H	H
79	SO	O	H	H	H	H	H
80	SO ₂	O	H	H	H	H	H
81	SO ₂	O	4-Cl	H	H	H	H

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TABLE 1 continued

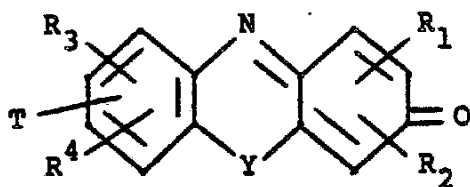
Number	Y	X	R ₁	R ₂	R ₃	R ₄	T
82	N—Me	O	H	H	H	H	H
83	N—Me	O	4-Cl	H	H	H	H
84	N—Me	O	4-Cl	H	7-OMe	H	H
85	N—Me	O	4-Br	H	7-OMe	2-OMe	H
86	NCN	O	4-Br	H	7-OMe	2-OMe	H
87	NCN	O	4-Cl	H	H	H	H
88	NH	O	2-Cl	H	H	H	H
89	NH	O	4-Cl	H	H	H	H
90	S	O	2-t-Bu	4-t-Bu	H	H	H
91	S	O	2-t-Bu	4-t-Bu	9-OMe	H	H
92	S	O	2-t-Bu	4-t-Bu	7-F	H	H
93	S	O	2-t-Bu	4-t-Bu	7-Me	H	H
94	S	O	2-t-Bu	4-t-Bu	7-SMe	H	H

*p-PAA = para-phenylacetic acid

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TABLE 2

Compounds of the Formula



Number	Y	R ₁	R ₂	R ₃	R ₄	T
95	S	H	H	H	H	H
96	S	2-Cl	H	H	H	H
97	S	H	H	6-Cl	H	H
98	S	H	H	7-Cl	H	H
99	S	H	H	8-Cl	H	H
100	S	H	H	9-Cl	H	H
101	S	1-Cl	H	H	H	H
102	S	1-Cl	4-Cl	H	H	H
103	S	2-Cl	4-Cl	H	H	1-Cl
104	S	2-N(Me) ₂	H	H	H	H
105	S	2-SMe	H	H	H	H
106	S	2-S-pPAA	H	H	H	H
107	S	2-C(O)CH ₃	H	H	H	H
108	S	2-OMe	H	H	H	H
109	S	H	H	H	7-CH ₂ CO ₂ H	H
110	S	H	H	H	8-CH ₂ COOH	H
111	S	H	2-SO ₃	H	H	H
112	S	2-N(Me) ₂	H	H	H	H
113	S	2-SMe	H	H	H	H
114	S	2-C(O)CH ₃	H	H	H	H
115	S	2-OMe	H	H	H	H
116	S	2-CH ₂ CO ₂ H	H	H	H	H
117	S	2-CH(CH ₃)CO ₂ H	H	H	H	H
118	S	4-CH ₂ COOH	H	H	H	H
119	S	4-CH(CH ₃)CO ₂ H	H	H	H	H
120	S	H	H	7-OH	6-propyl	H

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TABLE 2 continued

Number	Y	R ₁	R ₂	R ₃	R ₄	T
121	S	4-Cl	H	H	H	H
122	S	4-F	H	H	H	H
123	S	4-F	H	7-Cl	H	H
124	S	4-Et	H	H	H	H
125	S	4-Et	H	7-OMe	H	H
126	S	4-Et	H	7-Cl	H	H
127	S	4-Cl	H	7-OMe	H	H
128	S	4-OMe	H	7-Cl	H	H
129	S	4-Cl	H	6-Cl	H	H
130	S	4-Cl	H	8-Cl	H	H
131	S	4-Cl	H	9-Cl	H	H
132	S	4-Cl	H	6-OMe	H	H
133	S	4-Cl	H	8-OMe	H	H
134	S	4-Cl	H	9-Et	H	H
135	S	4-Cl	H	6-Et	H	H
136	S	4-Cl	H	7-Et	H	H
137	S	4-Cl	H	8-Et	H	H
138	S	4-Cl	1-Et	H	H	H
139	S	4-Cl	2-Et	H	H	H
140	S	4-Cl	1-CH ₂ COOH	H	H	H
141	S	4-Cl	2-CH ₂ COOH	H	H	H
142	S	4-Cl	H	6-CH ₂ COOH	H	H
143	S	4-Cl	H	7-CH ₂ COOH	H	H
144	S	4-Cl	H	8-CH ₂ COOH	H	H
145	S	4-Cl	2-N(Me) ₂	H	H	H
146	S	4-Cl	1-N(Me) ₂	H	H	H
147	S	4-Cl	2-N(Me) ₂	7-OMe	H	H
148	S	4-Cl	2-N(Me) ₂	7-Cl	H	H
149	S	4-Cl	2-SMe	H	H	H
150	S	4-Cl	2-SCH ₂ COOH	H	H	H

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TABLE 2 continued

Number	Y	R ₁	R ₂	R ₃	R ₄	T
151	S	4-Cl	2-S-pPAA	H	H	H
152	S	4-Cl	1-S-pPAA	H	H	H
153	S	4-Cl	2-S-pPAA	7-OMe	H	H
154	S	4-Cl	2-SO ₃ H	H	H	H
155	S	4-Cl	2-OMe	H	H	H
156	S	4-Cl	2-OMe	7-Cl	H	H
157	S	4-Cl	H	7F	H	H
158	S	4-OMe	H	7-OMe	H	H
159	S	4-OMe	H	7-Me	H	H
160	S	4-OMe	2-SMe	H	H	H
161	S	4-SMe	H	H	H	H
162	S	4-Br	H	H	H	H
163	S	4-I	H	H	H	H
164	S	4-Br	H	7-OMe	H	H
165	S	4-I	H	7-OMe	H	H
166	S	4-Br	2-Me	H	H	H
167	S	4-I	2-Me	H	H	H
168	S	4-Cl	H	7/8-(CH ₂) ₄ —		H
169	S	4-Cl	H	7/8-(CH ₂) ₃ —		H
170	S	4-Br	2-OMe	7-OMe	H	H
171	S	2-OMe	7-OMe	H	H	H
172	S	1-OMe	7-OMe	H	H	H
173	S	2-OMe	7-OMe	H	H	1-Br
174	S	1-OMe	7-OMe	H	h	2-Br
175	S	1-OMe	7-OMe	H	H	4-Br
176	S	1-OMe	7-OMe	H	H	2-Cl
177	S	1-OMe	7-OMe	H	H	4-Cl
178	S	2-OMe	7-OMe	H	H	1-Cl
179	S	2-OMe	7-OMe	H	H	4-Cl
180	S	2-OEt	7-OEt	H	H	1-Br


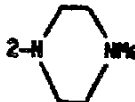
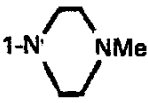


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TABLE 2 continued

Number	Y	R ₁	R ₂	R ₃	R ₄	T
181	S	2-OEt	7-OEt	H	H	4-Br
182	S	2-OEt	7-OEt	H	H	1-Cl
183	S	2-OEt	7-OEt	H	H	4-Cl
184	S	2-OMe	7-OMe	8-OMe	H	1-Br
185	S	2-OMe	7-OMe	8-OMe	H	4-Br
186	S	2-OMe	7-OMe	H	H	4-F
187	S	2-OMe	7-OMe	H	H	4-CF ₃
188	S	2-OMe	7-OEt	H	H	4-Br
189	S	2-OMe	7-OEt	H	H	4-Cl
190	S	2-OMe	7-OEt	H	H	4-F
191	S	2-OMe	7-OEt	H	H	4-CF ₃
192	S	2-OEt	7-OMe	H	H	4-Br
193	S	2-OEt	7-OMe	H	H	4-Cl
194	S	2-OEt	7-OMe	H	H	4-F
195	S	2-OEt	7-OMe	H	H	4-CF ₃
196	S	1-OMe	2-OMe	7-OMe	H	4-Br
197	S	1-OMe	2-OMe	H	H	H
198	S	1-OMe	2-OMe	H	H	4-Br
199	O	Same as Numbers 90—198				
200	SO ₂	4-OH	H	H	H	H
201	SO ₂	1-OMe	2-OMe	4-CH ₃	H	H
202	SO ₂	2-OMe	7-OMe	4-OH	H	H
203	SO ₂	2-OMe	4-OH	H	H	H
204	SO ₂	1-OMe	4-OH	H	H	H
205	SO ₂	2-Me	4-OH	H	H	H
206	SO ₂	2-Cl	4-OH	H	H	H
207	SO ₂	2-OEt	7-OEt	4-OH	H	H
208	SO ₂	2-SO ₂ Me	4-OH	H	H	H
209	SO ₂	4-OMe	H	H	H	H
210	SO ₂	2-OMe	4-OMe	7-OMe	H	H

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TABLE 2 continued

Number	Y	R ₁	R ₂	R ₃	R ₄	T
211	O	1-CO ₂ H	4-OH	7-NMe ₂	H	H
212	O	1-Cl	2-Cl	4-Cl	H	7-Cl
213	S	9-OMe	H	H	H	H
214	S	2-OMe	H	H	H	H
215	S	2-OMe	4-OMe	H	H	H
216	S	1-OMe	2-OMe	4-Me	H	H
217	S	4-OMe	H	H	H	H
218	S	1-OMe	7-OMe	H	H	4-Br
219	S	1-OMe	7-OMe	2-Cl	H	4-Cl
220	S	1-OMe	7-OMe	H	H	4-Cl
221	S		7-OMe	H	H	H
222	S		7-OMe	H	H	4-Br
223	SO ₂	2-OMe	4-OH	7-OMe	H	H
224	SO ₂	1-NHPr	4-NHPr	H	H	H
225	SO ₂			H	H	H
226	SO ₂	2-OMe		7-OMe	H	H
227	SO ₂	2-OMe	7-OMe	H	H	H
228	SO ₂	2-OMe	4-NHPr	7-OMe	H	H
229	S	1-NHPr	4-NHPr	H	H	H
230	S	1-NHPr	4-NHPr	7-OMe	H	H
231	S	1-NHPr	4-NHPr	H	H	H
232	S	2-NHPr	4-NHPr	7-OMe	H	H
233	S	2-OMe	4-NH ₂	7-OMe	H	H
234	S	2-OMe	4-NHPr	7-OMe	H	H

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TABLE 2 continued

Number	Y	R ₁	R ₂	R ₃	R ₄	T
235	O	1-OMe	4-Cl	7-OMe	H	H
236	O	1-OMe	4-Br	7-OMe	H	H
237	O	1-NHPr	4-NHPr	H	H	H
238	SO ₂	1-OMe	4-CN	7-OMe	H	H
239	SO ₂	2-OMe	4-NHCH ₂ CO ₂ R*	7-OMe	H	H
240	SO ₂	2-OMe	4-S-7-Bu	7-OMe	H	H
241	SO ₂	2-OMe	4-CH ₂ CO ₂ R*	7-OMe	H	H
242	SO ₂	2-OMe	4-SO ₂ Me	7-OMe	H	H
243	S	2-S-n-Bu	H	H	H	H
244	S	4-S-n-Bu	H	H	H	H
245	S	2-Me	4-S-n-Bu	H	H	H
246	S	2-OMe	7-Me	H	H	4-Br
247	S	2-OMe	7-CF ₃	H	H	4-Br
248	S	2-OMe	7-F	H	H	4-Br
249	S	2-OMe	7-Cl	H	H	4-Br
250	S	2-OMe	7-Br	H	H	4-Br
251	S	2-OMe	7-NMe ₂	H	H	4-Br
252	S	2-OMe	7-SMe	H	H	4-Br
253	S	2-OMe	7-SO ₂ Me	H	H	4-Br
254	S	2-OMe	7-Ph	H	H	4-Br
255	S	1-Me	H	H	H	H
256	S	2-Me	H	H	H	H
257	S	2-OEt	H	H	H	H
258	S	7-Cl	H	H	H	H
259	S	9-Cl	H	H	H	H
260	S	7-F	H	H	H	H
261	S	7-Me	H	H	H	H
262	S	7-OMe	H	H	H	H
263	S	2-Cl	H	H	H	H

*R is H or C₁C₄ alkyl.

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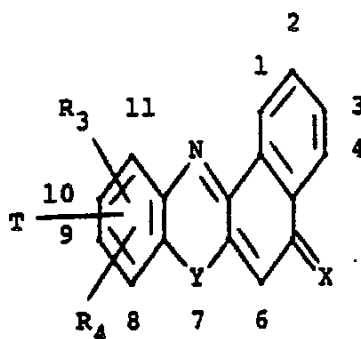
TABLE 2 continued

Number	Y	R ₁	R ₂	R ₃	R ₄	T
264	S	1-Me	7-Me	H	H	H
265	S	1-Me	7-Me	H	H	H
266	S	2-OMe	7-OEt	H	H	H
267	O	2-NH ₂	H	H	H	H
268	O	7-OH	H	H	H	H
269	O	COMe	H	H	H	H
270	SO ₂	2-OMe	7-OMe	H	H	4-Br
271	S	2-NHPr	4-NHPr	H	H	H
272	S	2-Cl	H	H	H	4-Cl
273	S	1-Me	7-Me	H	H	4-Cl

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TABLE 3

Compounds of the Formula



Example	Y	X	R ₃	R ₄	T
1	O	O	H	H	H
2	S	O	H	H	H
3	SO	O	H	H	H
4	SO ₂	O	H	H	H
5	SO	O	H	H	6-Cl
6	S	O	6-COCH ₃	H	H
7	S	O	6-CH ₃	H	H
8	SO ₂	O	6-OH	H	H
9	SO ₂	O	6-OMe	H	H
10	S	O	9-OMe	H	H
11	S	O	6-OH	H	H
12	S	O	6-OMe	H	H
13	S	O	6-NHCOMe	H	H
14	S	O	6-NHPh	H	H
15	S	O	H	H	6-Br
16	S	O	6-NHMe	H	H
17	S	O	6-NH-t-Bu	H	H
18	S	O	6-NH-COMe	H	9-Cl
19	S	O	6-NH-COMe	9-Ome	H
20	S	O	6-NHPh-p-Br	H	9-Cl
21	O	O	H	H	6-Cl
22	O	O	H	H	6-Br
23	O	O	9-OMe	H	6-Br

TABLE 3 continued

	Example	Y	X	R ₃	R ₄	T
5	24	O	O	9-OMe	6-NHPr	H
	25	S	O	6-CF ₃	H	H
10	26	S	O	6-S-n-Bu	H	H
	27	S	O	6-OMe	H	9-Cl
	28	S	O	9-OMe	H	6-Cl
15	29	S	O	6-OMe	9-OMe	H
	30	S	O	6-Cl	9-Me	11-Br
20	31	S	O	6-NHPh	9-Me	11-Br
	32	S	O	6-Me	H	H
	33	O	NH	9-NMe ₂	10-Me	H
25	34	O	NH	9-N(Et) ₂	H	H

A quite specific embodiment of the present invention is represented by the tripeptide γ -Glutamylcysteylglycine derivatives: 2-5-glutathionyl-3H-phenothiazin-3-one and 4-chloro-2-5-glutathionyl-phenothiazine-3-one.

The compounds of the Formula I have unexpected activity as inhibitors of the mammalian biosynthesis of leukotriene B₄, as well as leukotrienes C₄, D₄, E₄ and F₄, the active elements of the slow reacting substance of anaphylaxis (SRS—A). The compounds of Formula I act as inhibitors of the mammalian 5-Lipoxygenase enzyme system of the arachidonic acid cascade. This inhibition of the mammalian biosynthesis of leukotrienes indicated that the compositions would be useful to treat, prevent or ameliorate, in mammals and especially in humans 1) pulmonary conditions including diseases such as asthma, 2) allergies and allergic reactions such as allergic rhinitis, contact dermatitis, allergic conjunctivitis and the like, 3) inflammation such as arthritides, 4) pain, 5) skin conditions such as psoriasis and the like and 5) cardiovascular conditions such as angina.

Representative compounds of Formula I have been tested using one or more of the following assays to determine their mammalian leukotriene biosynthesis inhibiting activity and other relevant activities.

RBL—1 5-Lipoxygenase

Rat basophilic leukemia (RBL—1) cells were sonicated and centrifuged at 125000 xg. The resulting supernatant fraction was incubated with arachidonic acid (labelled with ¹⁴C) to convert a portion of it to ¹⁴C—5(S)-hydroxyicosatetraenoic acid (5—HETE). Compounds being evaluated as inhibitors of 5-Lipoxygenase were added prior to the addition of arachidonic acid. 5—HETE was isolated by extraction and paper chromatography, and quantitated by determining the amount of radioactivity (cpm) associated with 5-HETE.

Reference: Egan, R. W., Tischler, A. M. Baptista, E. H., Ham, E. A., Soderman, D. D., and Gale, P. H., *Advances in Prostaglandin, Thromboxane and Leukotriene Research* 11 151 (1983), (Samuelson, B., Ramwell, P. W., and Paoletti, R. (eds.), Raven Press, N.Y.

Mouse Macrophage Assay

Mouse peritoneal macrophages were treated sequentially with arachidonic acid (labelled with tritium); the compound being evaluated as an inhibitor, and a stimulator (zymosan). Metabolites derived from arachidonic acid (PGE₂, 6-keto PG-F_{1 α} and leukotriene C₄) were separated from the incubation medium by extraction and chromatography, and then quantitated by determining the amount of radioactivity (Cpm) associated with each of them. Inhibitors caused a reduction in the amount of radioactivity (cpm) associated with a given metabolite. (This protocol is identical to that described in the reference except that the radioactivity herein associated with the LTC₄ was determined by counting an aliquot of the final aqueous solution directly rather than chromatographing it first).

Reference: Humes, J. L. *et al.*, *J. Biol. Chem.* 257, 1591—4 (1982).

Antigen Challenge 'in vitro' Assay

Male guinea pigs weighing 300—350 g were sensitized by injecting (I.P.) ml of a suspension containing 0.4 mg of egg albumin (Ovalbumin, Grade V, Sigma Chemical Co.) and 4.0 g aluminum hydroxide in 19.6 ml of saline. Two weeks were permitted for sensitization to occur.

- 5 Three sensitized guinea pigs were stunned and exsanguinated. The tracheas were removed, freed of adhering tissue and divided longitudinally by cutting through the cartilaginous tissue directly opposite the muscle insertion. Each opened trachea was then transected between every second cartilage. Four of the cut sections were tied together, end to end, in a series with a No. 7 silk thread ensuring that the tracheal muscles were all in the same vertical plane. Thus, each chain consisted of tissue from three different

- 10 animals.
The chain so formed was then suspended under 1 g of tension (by silk ties at each end) in a 20 ml organ bath containing 10 ml of modified* Krebs-Henseleit buffer solution gassed with 95% O₂ and 5% CO₂ at 37°C. Mepyramine (0.55 µg/ml) and indomethacin (2.67 µg/ml) were added to the buffer to avoid the contribution of histamine receptors and cyclooxygenase products to the contraction. To record responses one end of the tracheal chain was attached to a Gould-Statham UC—2 force displacement transducer which

- 15 was connected to a Beckman Type R-dynograph. The preparations were allowed to equilibrate for one hour during which time the tissues were automatically washed (10 ml volume displacement) every 6 minutes.
After the equilibration period the tissues were primed with methacholine (3 µg/ml; 1.5×10^{-5} M), washed and allowed to recover to baseline. The tissues were treated again with a second dose of

- 20 methacholine, washed, allowed to return to baseline and washed for an additional hour.
Two chains were used as a control. These were incubated in a concentration of egg albumin sufficient to induce an average contraction of 50—80% of the methacholine response.

- Each compound to be tested was added to two other baths (at a final concentration in each bath of 10 µg/ml) 15 minutes prior to challenging the fresh chains with egg albumin.

- 25 The response of the challenged tissue was expressed as a percentage of the methacholine maximum. The % inhibition for each compound was then calculated. Compounds which at 10 µg/ml (final conc.) inhibited the egg albumin response by 50% or more were retested at a lower concentration.

Asthmatic Rat Assay

- 30 Rats were obtained from an inbred line of asthmatic rats. Both female and male rats from 200 to 300 g were used.

- Egg albumin (EA), grade V, crystallized and lyophilized, was obtained from Sigma Chemical Co., St Louis. *Bordetella pertussis* vaccine, containing 30×10^8 killed bacteria per ml was obtained from the Institut Armand-Frappier, Laval des Rapides, Quebec. Aluminum hydroxide was obtained from the Regis Chemical

- 35 Company, Chicago.
The challenge and subsequent respiratory recordings were carried out in a clear plastic box with internal dimensions $10 \times 6 \times 4$ inches. The top of the box was removable; in use, it was held firmly in place by four clamps and an airtight seal was maintained by a soft rubber gasket. Through the center of each end of the chamber a Devilbiss nebulizer (No. 40) was inserted via an airtight seal and each end of the box also had an outlet. A Fleisch No. 0000 pneumotachograph was inserted into one end of the box and coupled to a

- 40 Grass volumetric pressure transducer (PT5—A) which was then connected to a Beckman Type R Dynograph through appropriate couplers. While aerosolizing the antigen, the outlets were open and the pneumotachograph was isolated from the chamber. The outlets were closed and the pneumotachograph and the chamber were connected during the recording of the respiratory patterns. For challenge, 2 ml of a

- 45 3% solution of antigen in saline was placed into each nebulizer and the aerosol was generated with air from a small Potter diaphragm pump operating at 10 psi and a flow of 8 liters/minute.

- Rats were sensitized by injecting (s.c.) 1 ml of a suspension containing 1 mg EA and 200 mg aluminum hydroxide in saline. Simultaneously, they received an injection (i.p.) of 0.5 ml of *B. pertussis* vaccine. They

- were used between days 14 and 18 postsensitization. In order to eliminate the serotonin component of the

- 50 response, rats were pretreated intravenously 5 minutes prior to aerosol challenge with 30 mg/kg methylserzide. Rats were then exposed to an aerosol of 3% EA in saline for exactly 1 minute, then their respiratory profiles were recorded for a further 25—30 minutes. The duration of continuous dyspnoea was measured from the respiratory recordings.

- Compounds were generally administered either intraperitoneally 1 hour prior to challenge or orally 1½

- 55 hours prior to challenge. They were either dissolved in dimethylsulfoxide or suspended in 0.1% methocel and 0.5% Tween 80. The volume injected was 2 ml/kg (intraperitoneally) or 10 ml/kg (orally). Prior to oral treatment rats were starved overnight. Their activity was determined in terms of their ability to decrease the duration of symptoms of dyspnoea in comparison with a group of vehicle-treated controls. Usually, a compound was evaluated at a series of doses and an ED₅₀ was determined. This was defined as the dose

- 60 (mg/kg) which would inhibit the duration of symptoms by 50%.

*modified Krebs solution in grams/liter and (mM):

NaCl — 6.87 (120); glucose — 2.1 (11); NaHCO₃ — 2.1 (25); KCl — 0.32 (4.72); CaCl₂ — 0.28 (2.5); MgSO₄·7H₂O — 0.11 (0.5); KH₂PO₄ — 0.16 (1.2); pH at bathing solution = 7.35 ± 0.05 .

PAF-Induced Hyperalgesia Assay

Female Sprague-Dawley rats, 35—40 g were fasted overnight. Platelet activating factor, PAF, (L-lecithin B-acetyl O-alkyl) 1 µg/0.1 ml was given by subplantar injection in the rat paw. The compounds to be evaluated were homogenized in Aqueous Vehicle (0.9% benzyl alcohol, 0.5% Tween 80 and 0.4% methylcellulose) and administered orally in a volume of 0.1 ml, 30 minutes prior to PAF.

Animals were tested 1, 2, 3 and 4 hours after PAF administration. The vocalization threshold, defined as the pressure (mmHg) needed to evoke a squeak response, was recorded for both the injected and contralateral paw. No animal was subjected to pressure greater than 60 mmHg. Hyperalgesia is defined as a decrease in vocalization threshold as compared to a normal paw. Percent inhibition of hyperalgesia was calculated as the proportion of animals with vocalization thresholds greater than 200% of controls.

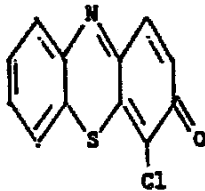
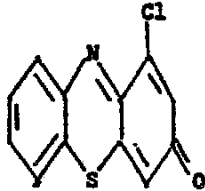


Brewer's Yeast Hyperalgesia Assay

The standard method* for yeast hyperalgesia was used. Female Sprague-Dawley rats, 35—40 g were fasted overnight. A 5% solution (volume 0.1 ml) of Brewer's yeast was injected into the rat paw. The compound was homogenized in aqueous vehicle and given orally 2 hours after yeast. Vocalization thresholds were recorded 1 hours after drug (3 hours after yeast). Percent inhibition of hyperalgesia was determined by the proportion of animals with vocalization thresholds greater than 25 mmHg.

* Winter, C. A. *et al.*, *J. Pharm. Exp. Ther.* 150, 165—171 (1965).

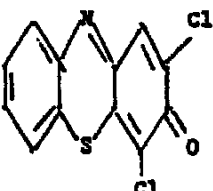
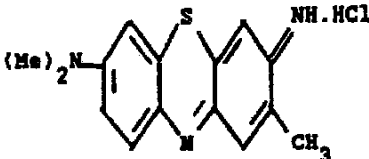


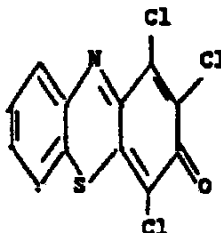
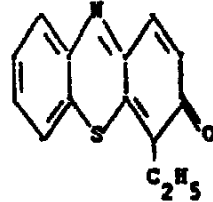
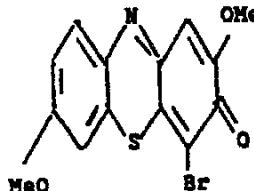
Following is data obtained using these various assays with representative compounds of Formula I.

TABLE 4
Assay Results

Test No.	Compound	Macrophage Ic50 (µg/ml)	RBL-1 Ic50 (µg/ml)	In Vitro Antigen Challenge Test µg/ml and % Inhibition
1		0.2	0.01	10 µg (100%) 1 µg (44%)
2		0.5	0.01	10 µg (68%)
3		0.2	—	10 µg (25%)
4		0.1	0.01	10 µg (100%) 1 µg (77%) 0.3 µg (42%)

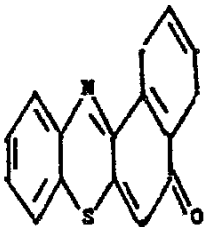
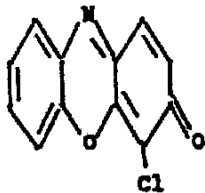
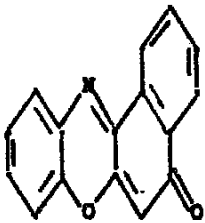
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TABLE 4 continued

Test No.	Compound	Macrophage lc50 ($\mu\text{g/ml}$)	RBL-1 lc50 ($\mu\text{g/ml}$)	In Vitro Antigen Challenge Test $\mu\text{g/ml}$ and % Inhibition
5		0.1—0.5	65% at 0.05 $\mu\text{g/ml}$	10 μg (45%)
6		10% at 0.05 $\mu\text{g/ml}$	—	10 μg 24%
7		15% at 0.5 $\mu\text{g/ml}$	—	10 μg 37%
8		33% at 0.1 $\mu\text{g/ml}$	—	—
9		75% at 5 $\mu\text{g/ml}$	—	—
10		—	—	10 μg (100%)
11		0.1	—	3 μg (23%)

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TABLE 4 continued

Test No.	Compound	Macrophage lc50 ($\mu\text{g/ml}$)	RBL-1 lc50 ($\mu\text{g/ml}$)	In Vitro Antigen Challenge Test $\mu\text{g/ml}$ and % Inhibition
12		0.1	—	10 μg (55%)
13		—	—	3 μg (54%)
14		0.1	—	—

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TABLE 5

Asthmatic Rat Assay Results

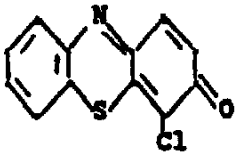
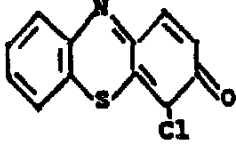
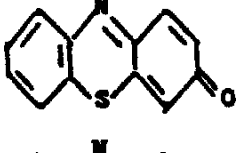
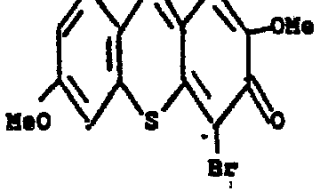
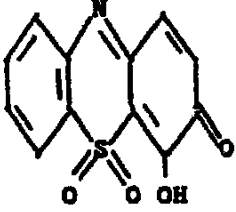
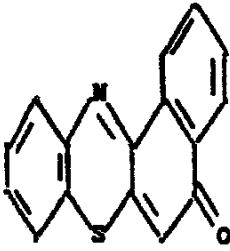
Test No.	Compound	Method of Administration	Ed ₅₀
A		i.p.	0.5 mg/kg
B		p.o.	1.5 mg/kg
C		i.p.	about 5.0 mg/kg
D		p.o.	1.0 mg/kg
E		p.o.	37% inhibition at 1.5 mg/kg
F		p.o.	36% inhibition at 5 mg/kg

TABLE 6

PAF-induced Hyperalgesia Assay for Compound
of Example 2

	Experiment 1	
	Vocalization Threshold ^a	% Inhibition
0.01 mg/kg p.o.	28.2 ± 5.2	40
0.03	40.2 ± 5.0	80
0.1	37.4 ± 3.9	80
0.3	45.4 ± 3.7	90
3.0	46.0 ± 3.0	100
Control	14.4 ± 1.6	

	Experiment 2	
	Vocalization Threshold ^a	% Inhibition
0.001 mg/kg p.o.	10.0 ± 1.6	0
0.003	16.4 ± 2.8	30
0.01	18.0 ± 2.9	30
0.1	29.6 ± 4.4	60
Control	11.2 ± 1.4	

^a mmHg Mean ± S.E.M., n = 10 Reading taken 3 hr. after
injection of PAF, (3.5 hr. after administration of
compound).

TABLE 7

Rat Brewer's Yeast Hyperalgesia Assay
for Example 2 Compound

Dose	Vocalization Threshold ^a	% Inhibition
0.3 mg/kg p.o.	17.6 3.1	30
1.0	19.4 3.1	30
3.0	30.0 5.8	60
10.0	28.6 3.0	70
30.0	32.6 3.3	80
Control	10.2 1.3	

^a mmHg: mean ± S.E.M. n = 10

The test results presented above show that representative compounds of Formula I inhibit the mammalian biosynthesis of leukotrienes especially via the 5-Lipoxygenase pathway of arachidonic acid metabolism and have representative pharmaceutical utility e.g., for asthma, pain and allergy.

The pharmaceutical compositions of the present invention will contain sufficient compound of Formula I in a dosage form suitable for inhibiting the mammalian biosynthesis of leukotrienes or, for the treatment desired. The effective concentration of the Formula I compound in the composition will vary as required by the mode of administration, dosage form and pharmacological effect and level desired. A general daily dosage of Formula I will range from 10 µg to 20 mg/kg of body weight. This dosage may be administered in single or divided individual doses. More or less of the general daily dosage may be necessary depending upon the individual needs of the patient.

For treating pulmonary conditions such as asthma, the mode of administration may be oral, parenteral, by inhalation, or by suppository. Suitable oral dosage forms are tablets, elixirs, emulsions, solutions and capsules, including delayed or sustained release capsules. Parenteral dosage forms include solutions and emulsions. Dosage forms for administration by inhalation include sprays and aerosols. These inhalation formulations may be administered in metered doses ranging from 0.1 µg to 200 µg, administered as needed.

For treating allergies or allergic reactions, such as allergic conjunctivitis and allergic rhinitis, the Formula I compound may be administered by any conventional mode, eg., orally, parenterally, topically, subcutaneously or by inhalation. The oral and parenteral dosage forms are the same type as for the pulmonary treatment. The topical application dosage forms include ointments, salves, controlled-release patches, emulsions, solutions, thixotropic formulations, powders and sprays. For topical application, the percent by weight active ingredient (Formula I compound) may vary from 0.001 to 10%.

For treating inflammation the mode of administration may be oral, parenteral or by suppository. The various dosage forms are the same as those described above.

For treating skin diseases such as psoriasis and atopic dermatitis, oral, topical or parenteral administration is useful. For topical application to the diseases area salves, patches, controlled release patches and emulsions are convenient dosage forms.

For use as an analgesic, i.e., for treating pain, any suitable mode of administration may be used, e.g., oral, parenteral, by insufflation or by suppository.

For treating cardiovascular conditions such as angina pectoris, any suitable mode of administration, e.g. oral, parenteral, topical or by insufflation, and dosage form, e.g. pills, liquid formulations, controlled release capsules or controlled release skin patches, may be used.

In addition to the common dosage forms set out above, the compound of Formula I may also be administered for the various utilities and indications or for inhibiting leukotriene synthesis by controlled release means and/or delivery devices such as those described in U.S. Patent Specifications US—A—3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Dosage forms for application to treat the eye are also disclosed in U.S. Patent Specification US—A—4,348,398.

In preparing suitable dosage forms, conventional compounding procedures and ingredients e.g. diluents or carriers, may be used. The following are examples of representative pharmaceutical dosage forms:

	<u>Injectible Suspension</u>	<u>mg/mL</u>
	Compound of Example C	1—100
45	Methylcellulose	5.0
	Tween 80	0.5
50	Benzyl alcohol	9.0
	Methyl paraben	1.8
	Propyl paraben	0.2
55	Water for injection to a total volume of 1 ml	
	<u>Aerosol for Oral Inhibition</u>	<u>mg/can (200 doses/can)</u>
60	Compound of Formula I	2—40
	Oleic Acid	0.2—4.0
	Trichloromonofluoro methane	5,000—8,000 To a total
65	Dichloromonofluoro methane	15,000—12,400 of 20,400

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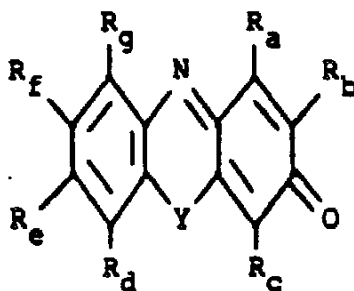
	<u>Cream</u>	<u>mg/g</u>
	Compound of Formula I	1—100
5	Cetyl alcohol	130.0
	Sodium Lauryl Sulfate	15.0
10	Propylene Glycol	100.0
	Methyl paraben	1.8
	Propyl paraben	1.2
15	Purified Water of sufficient quantity to make total 1 g	
	<u>Ointment</u>	<u>mg/g</u>
20	Compound of Formula I	1—100
	Methyl paraben	1.8
	Propyl paraben	1.2
25	Petrolatum of sufficient quantity to make total 1 g	
	<u>Tablet</u>	<u>mg/tablet</u>
30	Compound of Formula I	0.2—350
	Microcrystalline Cellulose	0—349.8
	Povidone	14.0
35	Microcrystalline Cellulose	90.0
	Pregelatinized Starch	43.5
40	Magnesium Stearate	2.5
		500
	<u>Capsule</u>	<u>mg/capsule</u>
45	Compound of Formula I	0.2—350
	Lactose Powder	248.5—598.3
50	Magnesium Stearate	1.5
		600

In addition to the compounds of Formula I, the pharmaceutical compositions can also contain other active ingredients, such as non-steroidal anti-inflammatory agents e.g. indomethacin, ibuprofen, sulindac and fenbufen, peripheral analgesic agents such as zomepirac and diflunisal, or cyclooxygenase inhibitors. They may also contain leukotriene antagonists such as those disclosed in European Patent Specifications EP—A—0,106,565, EP—A—0,104,885, EP—A—0,056,172 and EP—A—0,061,800 and in U.K. Patent Specification GB—A—2,058,785. These pharmaceutical compositions may also contain as the second active ingredient, antihistaminic agents such as benadryl, dramamine, histadyl and phenergan. Alternatively, they may include prostaglandin antagonists such as those disclosed in EP—A—0,011,067 or thromboxane antagonists such as those disclosed in US—A—4,237,160. The compounds of Formula I may also be advantageously combined with an H₁ or H₂-receptor antagonist, such as for instance cimetidine, ranitidine or terfenadine, or those disclosed in US—A—4,283,408; 4,362,736 and 4,394,508; and EP—A—0,040,696. These pharmaceutical compositions containing Formula I compound and a second

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active ingredient are another embodiment of the present invention. The weight ratio of the Formula I compound to the second active ingredient may be varied and may range from 10:1 to 1:10.

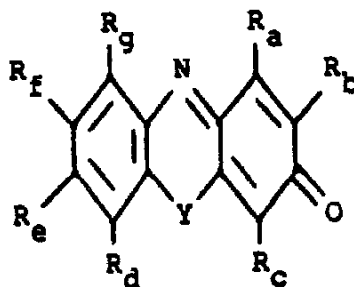
Another embodiment of the present invention are novel compounds encompassed by Formula I. These compounds have the Formula:



Tables 8 and 9 describe the novel compounds of the present invention:

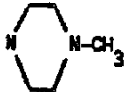
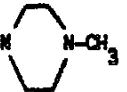
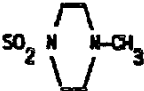

TABLE 8

Novel Formula I Compound




	Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
35	S	H	SCH ₃	H	H	H	H	H
	S	H	H	SCF ₃	H	H	H	H
	S	H	H	CHO	H	H	H	H
40	S	H	H	COCF ₃	H	H	H	H
	S	H	H	H	H	SCH ₃	H	H
45	S	H	H	H	H	CO ₂ CH ₃	H	H
	S	H	H	H	H	CO ₂ H	H	H
	S	H	H	H	H	CHO	H	H
50	S	H	H	H	H	CONH ₂	H	H
	S	H	H	H	H	CH ₂ OH	H	H
55	S	H	H	Cl	H	CO ₂ Me	H	H
	S	H	H	Cl	H	CO ₂ H	H	H
	S	H	H	Cl	H	CHO	H	H
60	S	H	H	Cl	H	CONH ₂	H	H
	S	H	H	Cl	H	CH ₂ OH	H	H
65	S	H	O-benzyl	Cl	H	H	H	H

TABLE 8 continued

Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	H	OEt	H	H	CH ₃	H	H
S	CH ₃	H	Cl	H	CH ₃	H	H
S	H	CH ₃	Cl	H	CH ₃	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	h	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
S	H	CH ₃	I	H	H	H	h
SO ₂	H	H	OH	H	H	H	H
SO ₂	H	OMe	OH	H	OMe	H	H
SO ₂	OMe	OMe	Me	H	H	H	H
SO ₂	H	H	OMe	H	H	H	H
SO ₂	H	OMe	OM	H	OMe	H	H
S	OCH ₃	OCH ₃	Me	H	H	H	H
S	H	H	COCH ₃	H	H	H	H
S	OCH ₃	H	Br	H	OCH ₃	H	H
S	OCH ₃	Cl	Cl	H	OCH ₃	H	H
S	OCH ₃	H	Cl	H	OCH ₃ H	H	H
S	H		H	H	OCH ₃	H	H
S	H		Br	H	OCH ₃	H	H
SO ₂	H	OCH ₃	OH	H	OCH ₃	H	H
SO ₂	NHPr	H	NHPr	H	H	H	H
SO ₂		H		H	H	H	H

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TABLE 8 continued

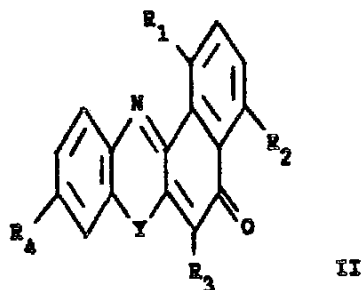
Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
SO ₂	H	OCH ₃		H	OCH ₃	H	H
SO ₂	H	OCH ₃	Br	H	OCH ₃	H	H
S	NHPR	H	NHPr	H	H	H	H
S	NHPr	N	NHPr	H	OCH ₃	H	H
S	H	NHPr	NHPr	H	H	H	H
S	H	NHPr	NHPr	H	OCH ₃	H	H
S	H	OCH ₃	NH ₂	H	OCH ₃	H	H
S	H	OCH ₃	NHPr	H	OCH ₃	H	H
SO ₂	H	OCH ₃	NHPr	H	OCH ₃	H	H
O	OCH ₃	H	Cl	H	OCH ₃	H	H
O	OCH ₃	H	Br	H	OCH ₃	H	H
O	NHPr	H	NHPr	H	H	H	H
SO ₂	H	OCH ₃	CN	H	OCH ₃	H	H
SO ₂	H	OCH ₃	NHCH ₂ CO ₂ R*	H	OCH ₃	H	H
SO ₂	H	OCH ₃	S-N-Bu	H	OCH ₃	H	H
SO ₂	H	OCH ₃	CH ₂ CO ₂ R*	H	OCH ₃	H	H
SO ₂	H	OCH ₃	SO ₂ CH ₃	H	OCH ₃	H	H
S	H	S-n-Bu	H	H	H	H	H
S	H	H	S-n-Bu	H	H	H	H
S	H	CH ₃	S-n-Bu	H	H	H	H
S	H	OMe	Br	H	CF ₃	H	H
S	H	OMe	Br	H	F	H	H
S	H	OMe	Br	H	Cl	H	H
S	H	OMe	Br	H	Br	H	H
S	H	OMe	Br	H	NMe ₂	H	H
S	H	OMe	Br	H	SMe	H	H
S	H	OMe	Br	H	SO ₂ Me	H	H
S	H	OMe	Br	H	Ph	H	H
S	H	H	H	Cl	OMe	H	H
S	H	OMe	Br	H	Me	H	H

* R is H or C₁—C₄ alkyl.

Table 9 describes the novel compounds of the present invention having four rings.

TABLE 9

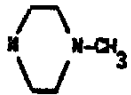
Novel Compounds of Formula II



Y	R ₁	R ₂	R ₃	R ₄
S	H	H	S-n-CH ₄ H ₉	H
S	OH	H	CH ₃	H
S	OCH ₃	H	CH ₃	H
S	H	H	F	H
S	H	H	CF ₃	H
S	H	H	Cl	CF ₃
S	H	H	Cl	SCH ₃
S	H	H	Br	Cl
S	H	H	CH ₃	Br
S	H	H	F	Br
S	H	H	COCH ₃	Cl
S	H	H	CF ₃	CH ₃
S	H	H	S-n-C ₄ H ₉	CH ₃
S	H	H	CF ₃	Cl
S	H	H	Cl	*CH ₂ COOR
S	H	H	Cl	*CH(Me)CO ₂ R
S	H	H	Cl	COCH ₃
S	H	H	H	Cl
S	H	H	H	Br
S	H	H	H	F
S	H	H	H	CF ₃
S	H	H	H	CH ₃
S	H	H	H	CH ₂ OH

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TABLE 9 continued

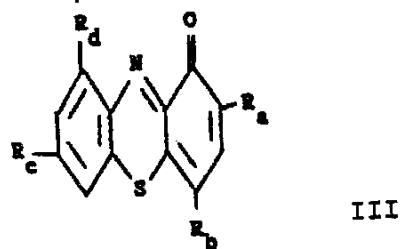
	Y	R ₁	R ₂	R ₃	R ₄
5	S	H	H	H	OCH ₃
	S	H	H	H	SCH ₃
10	S	H	H	H	*COOR
	S	H	H	H	*CH ₂ CO ₂ R
	S	H	H	H	*CH(Me)CO ₂ R
15	SO ₂	H	H	NHPr	H
	SO ₂	H	H		H
20	SO ₂	H	H	NH ₂	H
	SO ₂	H	H	NHPr	OCH ₃
25	S	-1,4-dihydro-		H	
	S	H	H	NHPr	OCH ₃
30	O	H	H	Cl	H
	O	H	H	Br	H
	O	H	H	Br	OCH ₃
35	O	H	H	NHPr	OCH ₃

*R is H or C₁₋₄alkyl.

Table 10 describes additional novel compounds of the present invention.

TABLE 10

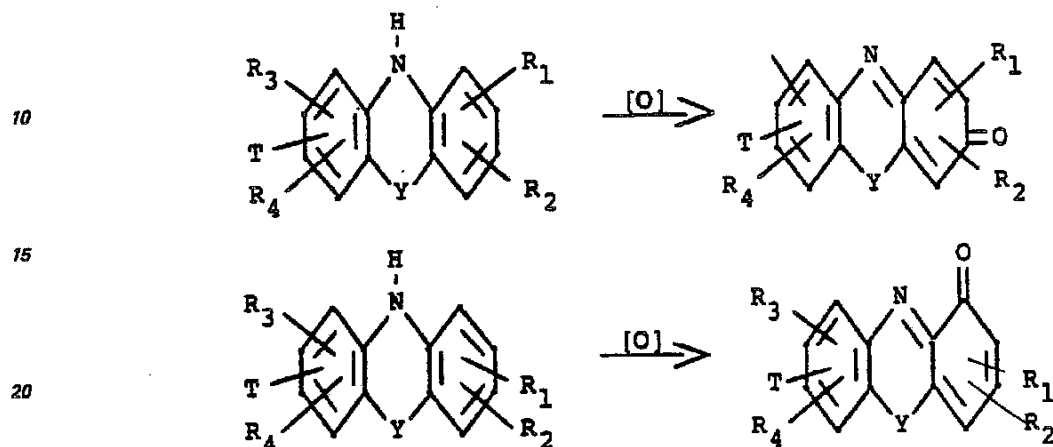
Novel Compounds of Formula III



	R _a	R _b	R _c	R _d
55	t-Bu	t-Bu	H	h
	t-Bu	t-Bu	F	H
60	t-Bu	t-Bu	Me	H
	t-Bu	t-Bu	SMe	H
65	t-Bu	t-Bu	H	OMe

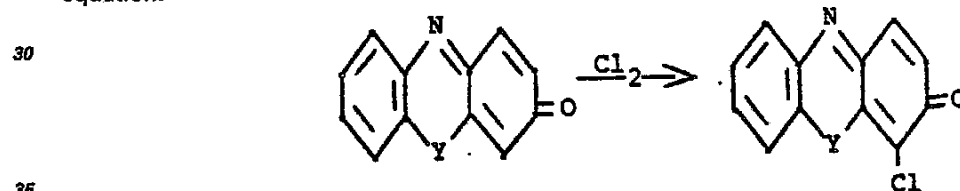
Formula I includes both novel and known compounds. These compounds may be prepared by any process available to the skilled artisan.

One such process for compounds where X = 0 involves the oxidation of the appropriate phenothiazine as illustrated by the following equations.

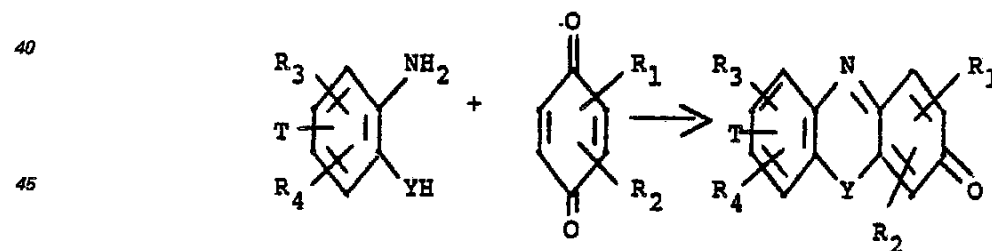


25 Various oxidizing agents and systems are taught in the art, e.g. PbO_2 , HNO_3 , $K_2Cr_2O_7$, $K_2Cr_2O_7$, iodine or $FeCl_3$.

Another process useful for preparing some Formula I compounds containing halogen substituents is by direct halogenation of an appropriate phenothiazone or analog thereof as illustrated by the following equation.

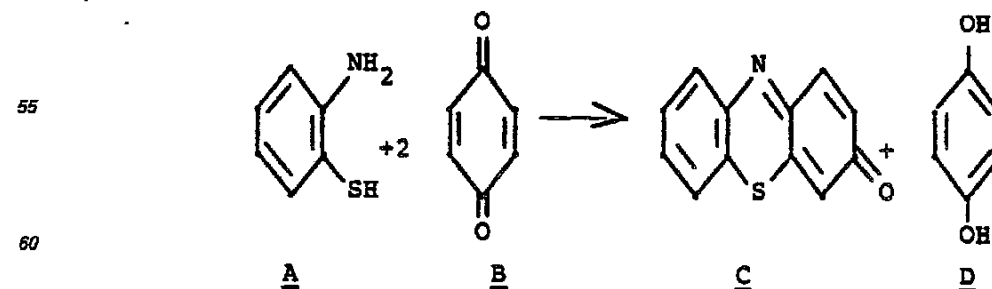


Still another process useful for preparing many of the Formula I compounds is by the reaction of an appropriate aniline with an appropriate quinone as illustrated by the following equation:



This general process is described in the literature.

50 A specific process for preparing the intermediate phenothiazin-3-one is illustrated by the following equation:



65 The process requires the use of 2 moles of quinone per mole of aniline. Any suitable solvent may be used. Example of such solvents are acetic acid, lower alkanols, acetic acid/ H_2O , loweralkanol/water or other polar solvents. A preferred solvent is one which will dissolve A , B and D and in which C is substantially insoluble.

The reaction is readily carried out at room temperature — lower temperatures, e.g. as low as -10°C , may be used — elevated temperatures may also be used but are not required. This process is more fully described in European Patent Specification EP—A—0,149,297.

Another useful process to prepare certain of the compounds of the present invention is the oxidation of certain phenothiazines or benzo[a]phenothiazines by standard oxidizing agents such as potassium dichromate, NaClO_2 and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Several of these benzo[a]phenothiazines and phenothiazines are described in EP—A—0,138,481 and EP—A—0,136,893.

Examples of the Formulae I and II compounds follow. These examples are illustrative and are provided as an aid to understand the invention. All temperatures are in degrees Celsius and are uncorrected.

10

Example 1

Method A:

3H-Phenothiazin-3-one

To a stirred suspension of 1.72 kg (16 mol) of *p*-benzoquinone in 13 litres MeOH at room temperature was added slowly a solution of 1.0 kg (8 mol) of 2-aminothiophenol in 600 ml MeOH over a period of 1 hour. The resulting red mixture was stirred at room temperature for another 2 hours and then the product 3H-phenothiaz-3-one was filtered off. This 3H-phenothiazin-3-one was washed thoroughly with methanol and dried to give 1.07 kg of 3H-phenothiazin-3-one (61.49% yield), m.p. $157-159^{\circ}\text{C}$.

20 Method B:

To a stirring solution of 1.1 kg of ceric ammonium nitrate in 12.5 liters of H_2O and 1.25 liters of HOAc at 10°C was added dropwise a solution of 100 g of phenothiazine in 500 ml acetone over a period of 20 minutes. The resulting mixture was stirred for another 20 minutes and the product 3H-phenothiazin-3-one was then filtered off. The filtered 3H-phenothiazin-3-one was washed with water thoroughly and dried to give 92 g of crude 3H-phenothiazin-3-one. The crude 3H-phenothiazin-3-one was extracted with minimum volume of CH_2Cl_2 . Upon dilution of the CH_2Cl_2 solution with 10 times the volume of cyclohexane, a precipitate was formed which was filtered and dried to afford 35 g of 3H-phenothiazin-3-one.

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Example 2

4-Chloro-3H-phenothiazin-3-one

To a stirring solution of 500 g (2.34 mol) of 3H-phenothiazin-3-one in 12.5 liters of glacial acetic acid was added 1.25 kg of potassium dichromate. The mixture was stirred at room temperature for 1/2 hour. To this resulting mixture was then added 2.34 mol of a 1 M solution of chlorine in glacial acetic acid dropwise over a period of 4 hours. The progress of the reaction was monitored by tlc to ensure no excess chlorine was added. After addition of chlorine was completed the mixture was stirred at room temperature for another 1/2 hour and was then poured into 120 liters of H_2O with vigorous stirring. The 4-chloro-3H-phenothiazin-3-one precipitated was allowed to settle overnight. The majority of the aqueous solution was siphoned and discarded and the rest was filtered. The filtered precipitate was washed thoroughly with water and then rinsed with methanol and was allowed to dry to give 504 g crude 4-chloro-3H-phenothiazin-3-one which was recrystallized from toluene, m.p. 221° .

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Example 3

4-Chloro-2,7-dimethoxy-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 2,7-dimethoxy-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 264°C .
Analysis, calculated: C, 54.63; H, 3.27; N, 4.55; S, 10.42; Cl, 11.52.
Observed: C, 54.64; H, 3.31; N, 4.53; S, 10.60; Cl, 11.69.

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Example 4

4-Chloro-1,7-dimethyl-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 1,7-dimethyl-3H-phenothiazin-3-one for 3H-phenothiazin-3-one the title compound was obtained, m.p. $215-218^{\circ}\text{C}$.
Analysis, calculated: C, 60.98; H, 3.66; N, 5.08; S, 11.63; Cl, 12.86.
Observed: C, 60.78; H, 3.75; N, 4.99; S, 11.79; Cl, 13.01.

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Example 5

4-Chloro-2,7-dimethyl-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 2,7-dimethyl-3H-phenothiazin-3-one for 3H-phenothiazin-3-one the title compound was obtained, m.p. $193-195^{\circ}\text{C}$.
Analysis, calculated: C, 60.98; H, 3.66; N, 5.08; S, 11.63; Cl, 12.86.
Observed: C, 60.89; H, 3.79; N, 5.22; S, 11.63; Cl, 12.50.

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Example 6

4-Chloro-2-methyl-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 2-methyl-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 206°C.

5 Analysis, calculated: C, 59.66; H, 3.08; N, 5.35; S, 12.25; Cl, 13.55.
Observed: C, 59.59; H, 3.36; N, 5.32; S, 12.64; Cl, 13.27.

Example 7

4-Chloro-7-methyl-3H-phenothiazin-3-one

10 Following the procedure described in Example 2 but substituting 7-methyl-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 218°C.

Analysis, calculated: C, 59.66; H, 3.08; N, 5.35; S, 12.25; Cl, 13.55.
Observed: C, 59.48; H, 3.17; N, 5.27; S, 12.40; Cl, 13.63.

Example 8

4-Chloro-7-ethoxy-2-methoxy-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 7-ethoxy-2-methoxy-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 236—239°C.

15 Analysis, calculated: C, 55.99; H, 3.76; N, 4.35; S, 9.96; Cl, 11.02.
20 Observed: C, 56.05; H, 3.93; N, 4.37; S, 10.11; Cl, 10.99.

Example 9

4-Bromo-2-methyl-3H-phenothiazin-3-one

25 Following the procedure described in Example 2 but substituting 2-methyl-3H-phenothiazin-3-one for 3H-phenothiazin-3-one and substituting bromine for chlorine, the title compound was obtained, m.p. 190°C.

Analysis, calculated: C, 50.99; H, 2.63; N, 4.57; S, 10.47; Br, 26.09.
Observed: C, 50.97; H, 2.69; N, 4.61; S, 10.56; Br, 26.24.

Example 10

9-Methoxy-3H-phenothiazin-3-one

30 To a suspension of p-benzoquinone (3.0 g) in 15 ml methanol was added 2-amino-3-methoxythiophenol (2.2 g) dissolved in 10 ml methanol. The mixture was stirred at room temperature for 45 minutes and concentrated *in vacuo*. The residue was triturated with ether and filtered. The resulting dark solid was chromatographed on silica gel and eluted with EtOAc, to afford the desired compound, m.p. 206—207°.

35 Analysis, calculated: C, 64.18; H, 3.73; N, 5.76; S, 13.18.
Observed: C, 64.10; H, 3.83; N, 5.69; S, 13.40.

Example 11

7-Fluoro-3H-phenothiazin-3-one

40 Following the procedure described in Example 10 but substituting 2-amino-5-fluorothiophenol for 2-amino-3-methoxythiophenol, the title compound was obtained, m.p. 240°C.

Analysis, calculated: C, 62.33; H, 2.61; N, 6.06; S, 13.86; F, 8.21.
Observed: C, 62.26; H, 2.70; N, 6.05; S, 14.04; F, 8.06.

Example 12

4-Chloro-7-fluoro-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 7-fluoro-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 250—255°C.

50 Analysis, calculated: C, 54.25; H, 1.90; N, 5.27; S, 12.07; F, 7.15; Cl, 13.34.
Observed: C, 54.10; H, 2.01; N, 5.35; S, 12.20; F, 7.20; Cl, 13.50.

Example 13

7-Fluoro-2-methoxy-3H-phenothiazin-3-one

55 Following the procedure described in Example 10 but substituting 2-amino-5-fluorothiophenol for 2-amino-3-methoxythiophenol and substituting 2-methoxy-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 252°C.

Analysis, calculated: C, 59.76; H, 3.08; N, 5.36; S, 12.27; F, 7.26.
Observed: C, 59.60; H, 3.11; N, 5.20; S, 12.17; F, 7.33.

Example 14

2,4-Dimethoxy-3H-phenothiazin-3-one

60 Following the procedure described in Example 10 but substituting 2-aminothiophenol for 2-amino-3-methoxythiophenol and substituting 2,6-dimethoxy-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 193°C.

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Analysis, calculated: C, 61.52; H, 4.06; N, 5.12; S, 11.73.
Observed: C, 61.37; H, 4.14; N, 5.16; S, 12.90.

Example 15

1,2-Dimethoxy-4-methyl-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-aminothiophenol for 2-amino-3-methoxythiophenol and substituting 2,3-dimethoxy-5-methyl-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 138°C.

Analysis, calculated: C, 62.70; H, 4.56; N, 4.87; S, 11.16.

Observed: C, 62.72; H, 4.74; N, 4.92; S, 11.28.

Example 16

1,7-Dimethyl-3H-phenothiazin-3-one and 2,7-dimethyl-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-amino-5-methylthiophenol for 2-amino-3-methoxythiophenol and substituting 2-methyl-p-benzoquinone for p-benzoquinone, a mixture of the title compounds were obtained. Chromatography on silica gel eluting with 10% EtOAc in CH₂Cl₂ afforded firstly 2,7-dimethyl-3H-phenothiazin-3-one, m.p. 177°C.

Analysis, calculated: C, 69.70; H, 4.60; N, 5.81; S, 13.29.

Observed: C, 69.51; H, 4.82; N, 5.78; S, 12.27,

and secondly, 1,7-dimethyl-3H-phenothiazin-3-one, m.p. 168—170°C.

Analysis, calculated: C, 69.70; H, 4.60; N, 5.81; S, 13.29.

Observed: C, 69.59; H, 4.63; N, 5.80; S, 13.40.

Example 17

2,4-Dichloro-7-fluoro-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-amino-5-fluorothiophenol for 2-amino-3-methoxythiophenol and substituting 2,6-dichloro-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 256—258°C.

Analysis, calculated: C, 48.02; H, 1.34; N, 4.68; S, 10.68; F, 6.33; Cl, 23.62.

Observed: C, 47.93; H, 1.42; N, 4.63; S, 10.75; F, 6.42; Cl, 23.80.

Example 18

1,4-Dichloro-7-fluoro-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-amino-5-fluorothiophenol for 2-amino-3-methoxythiophenol and substituting 2,5-dichloro-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 245—247°C.

Analysis, calculated: C, 48.02; H, 1.34; N, 6.33.

Observed: C, 48.20; H, 1.14; N, 6.20.

Example 19

2-Methoxy-7-methylthio-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-amino-5-methylthio thiophenol for 2-amino-3-methoxythiophenol and substituting 2-methoxy-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 222—224°C.

Analysis, calculated: C, 58.11; H, 3.83; N, 4.84; S, 22.16.

Observed: C, 58.28; H, 4.24; N, 4.62; S, 22.02.

Example 20

4-Trifluoromethyl-3H-phenothiazin-3-one and 2,4-bis(trifluoromethyl)-3H-phenothiazin-3-one

A solution of 3H-phenothiazin-3-one (10 g), trifluoromethyl iodide (50 g) and pyridine (40 ml) in acetonitrile (140 ml) was irradiated with a 450 watt lamp for 3 days. The volatiles were removed under vacuum and the resulting residue chromatographed on a silica gel column eluting with 5% EtOAc/CH₂Cl₂ to afford firstly, 2,4-bis(trifluoromethyl)-3H-phenothiazin-3-one (650 mg) m.p. 173—175°C.

Analysis, calculated: C, 48.14; H, 1.44; N, 4.01; S, 9.18; F, 32.64.

Observed: C, 48.25; H, 1.72; N, 4.00; S, 9.28; F, 32.51.

Secondly, 4-trifluoromethyl-3H-phenothiazin-3-one (1.76 g), m.p. 184—185°C.

Analysis, calculated: C, 55.51; H, 2.15; N, 4.98; S, 11.40; F, 20.27.

Observed: C, 55.60; H, 2.14; N, 5.22; S, 11.43; F, 20.41.

Example 21

4-Acetyl-3H-phenothiazin-3-one

A solution of 3H-phenothiazin-3-one (2 g) and acetaldehyde (32 ml) in benzene (240 ml) was irradiated with a 450 watt lamp for 2 days. The volatiles were removed under vacuum and the residue chromatographed on a silica gel column eluting with 25% EtOAc/hexane to afford the desired compound, m.p. 222°C.

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Analysis, calculated: C, 65.87; H, 3.55; N, 5.49; S, 12.56.
Observed: C, 65.88; H, 3.61; N, 5.30; S, 12.70.

Example 22

4-Bromo-2,7-dimethoxy-3H-phenothiazin-3-one

Step 1:

2-Methoxy-p-benzoquinone

Vanillin (2.432 kg) was added to a solution of sodium hydroxide (640 g) in water (8 l) and cooled to 10°C with an ice-bath. Then a solution of hydrogen peroxide (30%) (2.4 l) was added at a rate to keep the temperature of the reaction mixture below 30°C. The addition completed (about 2 hours), the reaction mixture was added over a period of 3 hours to a suspension of sodium periodate (880 g) in water (4 l) and acetic acid (640 ml) cooled with an ice-bath to 10°C (the temperature of the reaction mixture was kept below 35°C). The precipitate was filtered, washed with cold water followed by ethanol/hexane (1:1) mixture and air-dried to afford the title compound (1.9 kg), m.p. 144—147°C.

Step 2:

2-Amino-5-methoxythiophenol

To a solution of potassium hydroxide 8N (1.3 l) was added 2-amino-6-methoxybenzothiazole (750 g) and the mixture was refluxed for 18 hours. The resulting solution was neutralized by the addition of concentrated HCl, to pH 8.0, then acetic acid to pH 6.0. The precipitate which formed was filtered and washed with water to afford the title compound which was used immediately in Step 3.

Step 3:

2,7-Dimethoxy-3H-phenothiazin-3-one

To a suspension of 2-methoxy-p-benzoquinone, (1.15 kg) (Step 1) in methanol (8 l) was added portionwise a suspension of 2-amino-5-methoxythiophenol (from Step 2) in methanol (6 l). The reaction mixture was stirred for 15 minutes at room temperature, filtered and the collected solid washed with methanol (8 l). The product isolated was swished with DMF (16 l) for 2 hours, filtered and air-dried. The crude material was dissolved in hot DMF (16 l) (130—140°C), filtered through Celite® and the filtrate cooled to room temperature. The crystals were filtered, washed with methanol (8 l) and air-dried to afford the title compound (703 g), m.p. 237—238°C.

Step 4:

4-Bromo-2,7-dimethoxy-3H-phenothiazin-3-one

A solution of bromine (280 g) in acetic acid (2.8 l) was added over a period of 30 minutes to a suspension of 2,7-dimethoxy-3H-phenothiazin-3-one (250 g) (Step 3) in acetic acid (7.5 l) and stirred for 2 hours. Methanol (12 l) was added and the mixture was stirred until the black suspension became an orange suspension. Then, the precipitate was filtered, washed with methanol and air-dried to afford the desired compound (312 g), m.p. 260—261°C.

Analysis, calculated: C, 47.74; H, 2.86; N, 3.98; S, 9.10; Br, 22.69.

Observed: C, 47.74; H, 2.81; N, 3.90; S, 9.02; Br, 22.37.

Example 23

4-Chloro-2-ethoxy-3H-phenothiazin-3-one and 4-chloro-2,7-diethoxy-3H-phenothiazin-3-one

Metallic sodium (506 mg) was dissolved in absorbed ethanol (75 ml) and 4-chloro-3H-phenothiazin-3-one (4.95 g) was added and stirred overnight at room temperature. The solvent was removed in vacuo, the resulting residue stirred in acetone (500 ml) for 1 hour and filtered. The filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column eluting with 5% EtOAc/toluene to afford firstly, 4-chloro-2-ethoxy-3H-phenothiazin-3-one (1.33 g), m.p. 188—189°C.

Analysis, calculated: C, 57.63; H, 3.45; N, 4.80; S, 10.99; Cl, 12.15.

Observed: C, 57.66; H, 3.54; N, 4.81; S, 11.16; Cl, 12.02.

and secondly, 4-chloro-2,7-diethoxy-3H-phenothiazin-3-one (110 mg), m.p. 227—228°C.

Analysis, calculated: C, 57.22; H, 4.20; N, 4.17; S, 9.55; Cl, 10.56.

Observed: C, 57.19; H, 4.35; N, 4.07; S, 9.62; Cl, 10.61.

Example 24

2-(n-Butylthio)-3H-phenothiazin-3-one

To a solution of 3H-phenothiazin-3-one (0.64 g) in 75 ml methanol was added thiethylamine (1.0 ml) and n-butanethiol (0.58 ml). The mixture was stirred at room temperature for 48 hours. Then 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.67 g) was added. The mixture was stirred at room temperature for 2 hours. The solvent was removed in vacuo. The residue was chromatographed on neutral alumina (Act III) and eluted with 15% EtOAc/hexane to afford the title compound (0.4 g), m.p. 133°C.

Analysis, calculated: C, 63.78; H, 5.02; N, 4.65.

Observed: C, 63.61; H, 5.04; N, 4.51.

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Example 25

4-(n-Butylthio)-3H-phenothiazin-3-one

To a solution of phenothiazin-3-one (0.21 g) in 20 ml THF was added triethylamine (0.28 ml) and n-butanethiol (0.2 ml). The mixture was refluxed for 15 hours and then cooled to room temperature. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.22 g) was added and the reaction was stirred for 2 hours at 25°. The solvent was removed *in vacuo*. The residue was chromatographed on neutral alumina (Act III) and eluted with 15% EtOAc/hexane to afford the title compound, m.p. 72°C.

Analysis, calculated: C, 63.78; H, 5.02; N, 4.05; S, 21.24.

Observed: C, 63.83; H, 5.07; N, 4.86; S, 21.06.

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Example 26

4-(n-Butylthio)-2-methyl-3H-phenothiazin-3-one

To a solution of 2-methyl-phenothiazin-3-one (0.23 g) in 12 ml dichloroethane was added triethylamine (0.8 ml) and n-butanethiol (0.7 ml). The mixture was stirred at room temperature for 72 hours. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.22 g) was added. The mixture was stirred at room temperature for 2 hours. The mixture was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was chromatographed on neutral alumina (Act III) eluting with 15% EtOAc/hexane to give the title compound (120 mg), m.p. 97°C.

Analysis, calculated: C, 64.75; H, 5.43; N, 4.44.

Observed: C, 64.62; H, 5.53; N, 4.43.

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Example 27

2-S-Glutathionyl-3H-phenothiazin-3-one

A mixture of phenothiazin-3-one (0.22 g), triethylamine (0.41 ml) and glutathione (0.3 g) in 1,2-dichloroethane (12 ml) was stirred at room temperature for 5 days. The solvent was removed *in vacuo*. The residue was dissolved in water and filtered. The filtrate was concentrated *in vacuo* and then chromatographed on XAD resin and eluted with water to give the title compound.

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Example 28

4-Chloro-2-S-glutathionylphenothiazin-3-one

Following the procedure of Example 27, but substituting 4-chloro-3H-phenothiazine-3-one for 3H-phenothiazin-3-one, the title compound was obtained.

Example 29

5H-Benzo[a]phenothiazin-5-one

Following the procedure described in Example 10 but substituting 2-aminothiophenyl for 2-amino-3-methoxythiophenyl and substituting 1,4-naphthoquinone for p-benzoquinone the title compound was obtained, m.p. 176—177°C.

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Example 30

6-Chloro-5H-benzo[a]phenothiazin-5-one

Following the procedure described in Example 2, but substituting 5H-benzo[a]phenothiazin-5-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 230—231°C.

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Example 31

6-Methyl-5H-benzo[a]phenothiazin-5-one

Following the procedure described in Example 10, but substituting 2-aminothiophenol for 2-amino-3-methoxythiophenol and substituting 2-methyl-1,4-naphthoquinone for p-benzoquinone, the title compound was obtained, m.p. 181°C.

Analysis, calculated: C, 73.62; H, 4.00; N, 5.05; S, 11.56.

Observed: C, 73.77; H, 4.16; N, 4.99; S, 11.69.

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Example 32

1-Hydroxy-6-methyl-5H-phenothiazin-5-one

Following the procedure described in Example 10 but substituting 2-aminothiophenol for 2-amino-3-methoxythiophenol and substituting 5-hydroxy-2-methyl-1,4-naphthoquinone for p-benzoquinone, the title compound was obtained, m.p. 226—228°C.

Analysis, calculated: C, 69.61; H, 3.78; N, 4.77; S, 10.93.

Observed: C, 69.66; H, 3.90; N, 4.66; S, 10.77.

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Example 33

1-Methoxy-6-methyl-5H-phenothiazin-5-one

Potassium *tert.*-butoxide (500 mg) was added to a suspension of 1-hydroxy-6-methyl-5H-benzo[a]phenothiazin-5-one (from Example 32) (500 mg) and methyl iodide (2 ml) in DMF (20 ml). After 30 minutes at room temperature, EtOAc (250 ml) was added followed by water (200 ml). The aqueous layer

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was decanted and the organic layer was dried and evaporated to dryness. The residue was treated with ether, filtered and air-dried to afford the desired product (420 mg), m.p. 170—171°C.

Analysis, calculated: C, 70.34; H, 4.26; N, 4.56; S, 10.43.

Observed: C, 70.37; H, 4.44; N, 4.45; S, 10.52.

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Example 34

4-Hydroxy-3H-phenothiazin-3-one-5,5-dioxide

To a suspension of 3-hydroxy-10H-phenothiazine-5,5-dioxide (1.75 g, 7 mmoles) in 2% aqueous sulfuric acid (25 ml) there was added, at room temperature, a solution of 80% sodium chlorite (3.17 g, 28 mmoles) in water (25 ml). The mixture was stirred for 15 minutes, then the red-orange precipitate was filtered to afford crude product (1.73 g). Purification was achieved by crystallization from DMF-methanol, m.p. 266° (dec.).

Analysis, calculated: C, 55.16; H, 2.70; N, 5.36; S, 12.27.

Observed: C, 54.68; H, 2.76; N, 5.38; S, 12.47.

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Example 35

4-Chloro-3H-phenoxazin-3-one

To a solution of 1.2 g of 3H-phenoxazin-3-one in acetic acid (25 ml) was added K₂Cr₂O₇ (3.7 g). A solution of chlorine in acetic acid was added dropwise to the resulting suspension. After disappearance of the starting material, as monitored by TLC, the reaction mixture was poured into 200 ml of H₂O and the resulting precipitate was filtered (1.2 g) and chromatographed on silica gel to yield the title compound.

Analysis, calculated: C, 62.22; H, 2.61; Cl, 15.30.

Observed: C, 62.10; H, 2.75; Cl, 15.24.

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Example 36

2,4-Di-t-butyl-1H-phenothiazin-1-one

To a solution of 4.4 gm of 3,5-di-t-butyl-1,2-benzoquinone in 20 ml of ether was added a solution of 1.25 g of 2-aminothiophenol in 5 ml of ether. After stirring for 1 hour at 25°, the reaction mixture was evaporated. The residue was purified by flash chromatography on silica gel using 2% ethyl acetate in benzene as eluent. There was thus obtained 860 mg of the title compound as dark blue plates, m.p. 137—141°.

Analysis, calculated: C, 73.81; H, 7.12; N, 4.30; S, 9.85.

Observed: C, 73.77; H, 7.33; N, 4.33; S, 9.85.

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Example 37

4-Bromo-1,7-dimethoxy-3H-phenothiazin-3-one

To a suspension of 1,7-dimethoxy-3H-phenothiazin-3-one (300 mg) in acetic acid (9 ml) was added a 0.63 M solution of Br₂ in acetic acid (1.92 ml). After 15 minutes, methanol was added and the solid filtered, washed with ether and air dried to afford the title compound (353 mg), m.p. 267—270°C (dec.).

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Example 38

4-Chloro-1,7-dimethoxy-3H-phenothiazin-3-one and 2,4-dichloro-1,7-dimethoxy-2H-phenothiazin-3-one

To a suspension of 1,7-dimethoxy-3H-phenothiazin-3-one (800 mg) in acetic acid (24 ml) was added a 1.15 M solution of Cl₂ in acetic acid (3.1 ml). After 15 minutes, methanol was added and the mixture was filtered, washed with ether and air dried to afford a mixture of the two title compounds (700 mg), which were separated on a silica gel column (EtOAc:CH₂Cl₂, 1:9), affording 4-chloro-1,7-dimethoxy-2H-phenothiazin-3-one, m.p. 278—280°C (dec.).

Analysis, Calculated: C, 54.64; H, 3.28; N, 4.55; S, 10.42; Cl, 11.52.

Observed: C, 54.44; H, 3.26; N, 4.62; S, 10.54; Cl, 11.48.

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and 2,4-dichloro-1,7-dimethoxy-3H-phenothiazin-3-one, m.p. 259—260°C (dec.) m/e 341.

Example 39

7-Methoxy-2-(4-methylpiperazin-1-yl)-3H-phenothiazin-3-one

A mixture of 7-methoxy-3H-phenothiazin-3-one (1.2 g) and N-methyl piperazine HCl (3.4 g) in DMF (20 ml) was heated at 100°C for 3 hours. Then NaIO₄ (1 g) was added and the reaction mixture was heated at 100°C for 1 hour. Ice-water was added to the reaction mixture followed by ethyl acetate. The aqueous layer was decanted, filtered and the filtrate basified with K₂CO₃ and extracted with ethyl acetate. The organic layer was evaporated to dryness, the resulting residue was dissolved in CH₂Cl₂, dried and evaporated to dryness to afford the crude final product (1.2 g) which was purified by chromatography on silica gel column eluting with 10% MeOH/CH₂Cl₂ to give the title compound, m.p. 208—209°.

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Example 40

4-Bromo-7-methoxy-2-(4-methylpiperazin-1-yl)-3H-phenothiazin-3-one

To a suspension of 7-methoxy-2-(4-methylpiperazin-1-yl)-3H-phenothiazin-3-one (500 mg) in acetic acid (10 ml) was added a solution of bromine in acetic acid (0.5 M) (6 ml) and stirred for 5 minutes. Hexane

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(100 ml) was added and the resulting precipitate was filtered. The solid was suspended in a mixture of aqueous K_2CO_3 (50 ml), EtOAc (100 ml) and methanol (20 ml) and stirred for 15 minutes. After filtration and decantation, the organic layer was washed with brine, dried and evaporated to dryness to afford the title compound (190 mg) m.p. 209—210° (dec.).

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Example 41

4-Bromo-2,7-dimethoxy-3H-phenothiazin-3-one-5,5-dioxide

Step 1:

4-Bromo-3-hydroxy-2,7-dimethoxy-10-H-phenothiazine

10 To a suspension of 4-bromo-2,7-dimethoxy-3H-phenothiazin-3-one (100 g) in a mixture of ethylacetate (2 l) and water (1 l) was added sodium hydrosulfite (200 g) in one batch with mechanical stirring. The orange reaction mixture was stirred for 15 hours under a nitrogen atmosphere. The resulting white reaction mixture was filtered and the precipitate washed with water under a nitrogen atmosphere to prevent air oxidation of the compound. The title compound (130 g) was obtained as a wet material and was used as
15 such in the next step (Step 2). An analytical sample was air dried, m.p. 185°C.

Analysis, Calculated: C, 47.74; H, 3.42; N, 3.95; S, 9.05; Br, 22.56.

Observed: C, 47.21; H, 3.39; N, 3.74; S, 8.76; Br, 22.44.

Step 2:

3-Acetoxy-4-bromo-2,7-dimethoxy-10-H-phenothiazine

20 Wet 4-bromo-3-hydroxy-2,7-dimethoxy-10-H-phenothiazine (130 g) (from step 1) was suspended in pyridine (230 ml). The mixture was cooled to 0°C in an ice-water bath. Acetic anhydride (195 ml) was then slowly added. The solution was left stirring at room temperature for 1/2 hour. The mixture was then concentrated under reduced pressure to approximately 1/3 of the original volume. Then a mixture of
25 ether:hexane, 1:1 (700 ml) was added, causing a large amount of crystals to appear. These crystals were filtered, washed with ether, and air dried, giving 51.4 g of pure 3-acetoxy-4-bromo-2,7-dimethoxy-10-phenothiazine. The mother liquors were reevaporated, and ether and hexane were added again, giving 36.37 of crude 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine m.p. 201—203°C.

Analysis, Calculated: C, 48.50; H, 3.56; N, 3.53; S, 8.09.

30 Observed: C, 48.31; H, 3.47; N, 3.47; S, 8.00.

Step 3:

3-Acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazin-5,5-dioxide

To 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazin (20 g) (from Step 2) in suspension in
35 CH_2Cl_2 :MeOH, (1:1) (500 ml), was added m-chloroperoxybenzoic acid (26.0 g). The reaction mixture rapidly became deep brown with the formation of a yellowish precipitate which corresponded to the intermediate sulfoxide on the 5-position. The mixture was heated at reflux for 18 hours. The solid was then filtered and washed with ether. Since there was still some sulfoxide remaining, the solid was suspended in ethanol:1,2-dichloroethane (500 ml) with 1.35 g of m-chloroperoxybenzoic acid and heated at reflux overnight (15
40 hours). The solid was then filtered and washed with ether and air dried giving 13.0 g of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide, m.p. 260°C.

Analysis, Calculated: C, 44.87; H, 3.29; N, 3.27; S, 7.49.

Observed: C, 44.82; H, 3.21; N, 3.18; S, 7.67.

45 Step 4:

4-Bromo-3-hydroxy-2,7-dimethoxy-10H-phenothiazin-5,5-dioxide

To a suspension of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide (10.0 g) in methanol (105 ml) was added a solution of 2N aqueous sodium hydroxide (74 ml) under a nitrogen atmosphere. After 20 minutes, the mixture was acidified with 10% v/v aqueous acetic acid (250 ml), causing
50 a large amount of compound to precipitate. The mixture was then diluted with water (105 ml) and the solid filtered, washed with water and ether and dried in a desiccator to afford quantitatively the title compound, m.p. 252—260°C (dec).

Step 5:

4-Bromo-2,7-dimethoxy-3H-phenothiazin-3-one-5,5-dioxide

55 To a stirred suspension of 4-bromo-3-hydroxy-2,7-dimethoxy-10H-phenothiazin-5,5-dioxide (from Step 4) (1 g) in THF (10 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.17 g). After 15 minutes, the mixture was filtered, the solid washed with ether and air dried. The solid was filtered through a silica gel pad with CH_2Cl_2 :EtOAc, 1:1, to afford the title compound (300 mg), m.p. 228—230°C (dec), m/e 383.

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Example 42

2,7-Dimethoxy-4-(4-methylpiperazin-1-yl)-3H-phenothiazin-3-one-5,5-dioxide

To a stirred suspension of 4-bromo-3-hydroxy-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide (1 g) in THF (10 ml) was added 2,3-dichloro-5,5-dicyano-1,4-benzoquinone (1.17 g). After a period of 20 minutes, N-methyl piperazine (1.44 ml) was slowly added. After 20 minutes, hexane was added to the mixture and the resulting precipitate was filtered, washed with ether and air dried. The compound was chromatographed using CH₂Cl₂:MeOH (9.5:0.5) as eluant, to afford the title compound (242 mg), m.p. 261°C (dec.).

Analysis; Calculated: C, 58.67; H, 5.83; N, 10.80; S, 8.24.
 10 Observed: C, 58.73; H, 5.67; N, 10.83; S, 8.56.

Example 43

4-Hydroxy-2,7-dimethoxy-3H-phenothiazin-3-one-5,5-dioxide

To a stirred suspension of 4-bromo-3-hydroxy-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide (100 mg) in THF (10 ml) was added water (0.1 ml) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.12 g). After 20 minutes, hexane was added and the solid was filtered, washed with ether and air dried to afford the title compound, m.p. 333—335°C (dec.).

Example 44

1,4-Bis(1-propylamino)-3H-phenothiazin-3-one-5,5-dioxide

To a solution of 3-hydroxy-10H-phenothiazine-5,5-dioxide (989 mg) in THF (50 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.82 g). The resulting green mixture was stirred at room temperature for 3 minutes, then there was added n-propyl amine (2.36 g). The mixture was stirred for 20 minutes and then filtered. The filtrate was evaporated to dryness and the residue chromatographed on a column of silica gel eluting with a 1:20 mixture of ethyl acetate and dichloromethane to afford the title compound as a purple solid (850 mg). Crystallization from methane afforded purple crystals (606 mg), m.p. 174—176°C.

Analysis, Calc'd: C, 60.14; H, 5.89; N, 11.69; S, 8.92.
 30 Found: C, 60.08; H, 5.93; N, 11.80; S, 8.71.

Example 45

1,4-Bis(4-methylpiperazin-1-yl)-3H-phenothiazin-3-one-5,5-dioxide

The procedure of Example 44 was used, substituting N-methyl piperazine for n-propyl amine to afford the title compound. It was crystallized from a toluene-hexane mixture to afford red crystals, m.p.: 247—249°C (dec.).

Analysis, Calc'd: C, 59.84; H, 6.16; N, 15.86; S, 7.26
 35 Found: C, 59.98; H, 6.35; N, 15.58; S, 7.1.

Example 46

6-(1-Propylamino)-5H-benzo[a]phenothiazin-5-one-7,7-dioxide

Step 1: 5-acetoxy-12H-benzo[a]phenothiazine

To a stirred solution of 5-hydroxy-12H-benzo[a]phenothiazine (50 g) in pyridine (115 ml) was added acetic anhydride (48 ml). The reaction was exothermic stirring was continued without cooling for 30 minutes, then the mixture was cooled to 10°C using an ice bath. The yellow crystalline solid was filtered and washed with ether to afford the title compound (23.4 g). The product was crystallized from ethyl acetate, m.p. 185—186°C.

Step 2: 5-acetoxy-12H-benzo[a]phenothiazine-7,7-dioxide

To a suspension of 5-acetoxy-12H-benzo[a]phenothiazine (10 g) in dichloromethane (125 ml), was added a solution of m-chloroperoxybenzoic acid (18 g) in methanol (125 ml). The mixture was refluxed for 2.5 hours, then after cooling to room temperature the insoluble solid was filtered to afford the desired sulfone (8.6 g). The solid was recrystallized from THF m.p. 284—287°C.

Analysis, Calc'd: C, 63.70; H, 3.86; N, 4.13; S, 9.45.
 55 Found: C, 63.67; H, 3.82; N, 4.20; S, 9.44.

Step 3: 5-hydroxy-12H-benzo[a]phenothiazine-7,7-dioxide

To a suspension of 5-acetoxy-12H-benzo[a]phenothiazine-7,7-dioxide (6.6 g) in methanol (200 ml), kept under a nitrogen atmosphere was added 2N aqueous sodium hydroxide solution (132 ml). The mixture was stirred at room temperature for 7 minutes, then there was added 10% acetic acid (200 ml) and water (300 ml). After 10 minutes of stirring the mixture was filtered to afford the title compound (5.68 g) as a pink solid. The solid was recrystallized from THF, m.p. 334°C (dec.).

Analysis, Calc'd: C, 63.70; H, 3.86; N, 4.13; S, 9.45.
 60 Found: C, 63.67; H, 3.82; N, 4.20; S, 9.44.

Step 4: 6-(1-Propyl amino)-5H-benzo[a]phenothiazin-5-one-7,7-dioxide

To a suspension of 5-hydroxy-12H-benzo[a]phenothiazine-7,7-dioxide (594 mg) in THF (10 ml) was added 2,3-dichloro 5,6-dicyano-1,4-benzoquinone (1.021 gram). The mixture was stirred at room temperature for 2 minutes, then there was added n-propyl amine (0.2 ml). The stirring was continued for 0.5 hour, then the mixture was evaporated to dryness. To the residue was added 50 ml dichloromethane and the mixture was stirred for 15 minutes and filtered. The filtrate was evaporated to dryness and the residue crystallized from a mixture of toluene and hexane to afford the title compound (442 mg) as a red-brown crystalline solid, m.p. 149—151°C (dec.).

Analysis, Calc'd: C, 64.75; H, 4.58; N, 7.95; S, 9.10.

Found: C, 64.66; H, 4.48; N, 7.95; S, 9.04.

Example 47

6-(4-Methyl piperazin-1-yl)-5H-benzo[a]phenothiazin-5-one-7,7-dioxide

The procedure of Example 46, Step 4 was used, substituting N-methyl piperazine for n-propyl amine, to afford the title compound, m.p. slow dec. from 183°C.

Analysis, Calc'd: C, 64.10; H, 4.87; N, 10.68; S, 8.15.

Found: C, 63.89; H, 4.90; N, 10.56; S, 8.10.

Example 48

6-Amino-5H-benzo[a]phenothiazin-5-one-7,7-dioxide

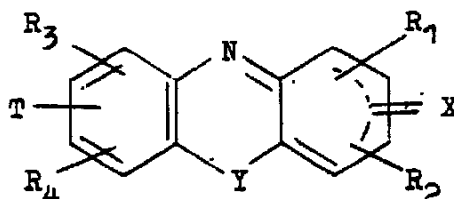
The procedure of Example 46, Step 4 was used, substituting 28% aqueous ammonium hydroxide solution for n-propyl amine, to afford the title compound, m.p. 264—266°C.

Certain of the compounds herein disclosed contain one or more centers of asymmetry. The present invention is meant to include the various diastereomers of such compounds as well as their racemic and optically active resolved forms.

Some of the compounds described may exist in one or more tautomeric forms. All such tautomeric forms are included within the present invention.

Claims

1. The use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of the Formula I, a compound that is a salt of a compound of the Formula I, or a pharmaceutical composition containing such a compound:



in which

X is in the 1 or 3 position and is O, S or NR;

R is H, C₁₋₆ branched or linear alkyl, CN or phenyl;

Y is O, Se, S, SO, SO₂ or NR; and the broken line represents a double bond between the 1 and 2 or 2 and 3 positions;

each of R₁, R₂, R₃ and R₄ independently of the others, is

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) C₂₋₆ alkenyl,
- (4) —(CH₂)_nM

where n is 0 or an integer from 1 to 6 and M is

- (a) OR₅,
- (b) halogen,
- (c) CF₃,

(d) SR₅ where R₅ is H; C₁₋₆ alkyl; benzyl; phenyl or substituted phenyl where the substituents are C₁₋₃ alkyl, halogen, CN, CF₃, COOR₆, CH₂COOR₆, (CH₂)_nNR₆R₉ where n is 0, 1 or 2, C₁₋₃ alkoxy, OH or C₁₋₆ haloalkyl; —(CH₂)_mCOOR₆, where m is 0 or an integer from 1 to 6 and R₆ is H, phenyl or C₁₋₆ alkyl; CN, formyl, CF₃ or CH₂—R₁₂, where R₁₂ is C₁₋₅ alkyl, phenyl or dimethylamino;

- (e) phenyl or substituted phenyl as defined above for R₅;
- (f) COOR₆;

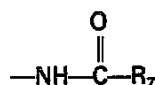


where R_{15} is H, $(CH_2)_n COOR_6$ where n is 0 or an integer from 1 to 4, C_{1-6} alkyl, CF_3 , phenyl, or substituted phenyl as defined above for R_5 ;

(h) tetrazole;

5

(i)



where R_7 is C_{1-6} alkyl, benzyl or phenyl;

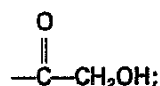
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(j) $-NR_8R_9$ where R_8 and R_9 are independently selected from H, phenyl or substituted phenyl as defined above for R_5 or C_{1-4} alkyl, C_{1-4} alkylaminoalkyl, or may be joined through the N to form a 4-methyl piperazinyl radical;

(k) $-NHSO_2R_{10}$ where R_{10} is OH, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl or CF_3 ;

15

(l)



20

(m) $-SOR_{11}$ where R_{11} is C_{1-6} alkyl, phenyl or substituted phenyl as defined above for R_5 , $(CH_2)_m COOR_6$ where m is 1 to 6, CN, formyl or CF_3 ;

(n) $-CONR_8R_9$;

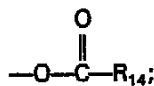
(o) $-SO_2NR_8R_9$;

(p) $-SO_2R_{13}$ where R_{13} is OH, H, C_{1-6} alkyl, phenyl or substituted phenyl as defined above for R_5 , $(CH_2)_m COOR_6$ where m is 1 to 6, CN or CF_3 ;

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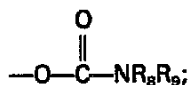
(q) NO_2 ;

(r)



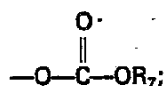
30

(s)



35

(t)



(u) $-CN$; or

(v) $NR_{15}R_{16}$ where R_{15} and R_{16} are such that $NHR_{15}R_{16}$ is an essential amino acid;

40 or any two of R_1 , R_2 , R_3 and R_4 are joined to form a fourth saturated or unsaturated C_{5-6} ring; and
T is H, halogen or CF_3 .

2. The use claimed in Claim 1, in which, in Formula I, X is in the 1-position.

3. The use claimed in Claim 2, in which X is O or NR.

4. The use claimed in Claim 3, in which, in Formula I, Y is S, SO, SO_2 , NR or O and, in the structural unit

45 $(CH_2)_nM$, n is 0 or 1.

5. The use claimed in Claim 4, in which, in Formula I, X is O and Y is S.

6. The use claimed in Claim 1, in which, in Formula I X is in the 3-position.

7. The use claimed in Claim 6, in which X is O or NR.

8. The use claimed in Claim 7, in which in Formula I Y is S, SO, SO_2 , NR or O and in the structural unit

50 $(CH_2)_nM$, n is 0 or 1.

9. The use claimed in Claim 8, in which Y is S or O.

10. The use claimed in Claim 9, in which X is O and Y is S.

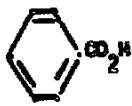
11. The use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of the Formula I, a compound that is a salt of a compound of the Formula I, or a

55 pharmaceutical composition containing such a compound, in which, in Formula I, the variables are as defined as follows, X being in the 1-position:


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Y	X	R ₁	R ₂	R ₃	R ₄	T
O	O	2-t-Bu	8-t-Bu	4-t-Bu	6-t-Bu	H
O	O	2-t-Bu	H	4-Me	H	H
S	S	2-t-Bu	4-t-Bu	H	H	H
N—CH ₃ , S, O, Se, SO or SO ₂	O	2-Cl	H	H	H	H
"	O	2-SCF ₃	H	H	H	H
"	O	2- 	H	H	H	H
S	O	2-t-Bu	4-t-Bu	H	H	H
N—CH ₃ , S, O, Se, SO or SO ₂	O	2-CN	H	H	H	H
"	O	H	3-CO ₂ Et	H	H	H
"	O	H	3-Cl	H	H	H
"	O	H	H	4-Cl	H	H
"	O	H	H	4-SO ₂ CH ₃	H	H
"	O	2-Cl	H	4-Cl	H	H
"	NH	2-Cl	H	4-Cl	H	H
"	NH	H	H	H	H	H
N—CN	O	2-Cl	H	4-Cl	H	H
S	O	H	H	H	H	H
S	O	2-Cl	3-Cl	4-Cl	7-Cl	9-Cl
S	O	2-Br	3-Br	4-Br	7-Br	9-Br
S	O	H	H	H	7-SO ₂ CH ₃	H
S	O	2-Cl	H	4-SO ₂ CH ₃	H	H
S	O	2-F	H	4-Cl	H	H
S	O	2-Br	H	H	H	H
S	O	2-CF ₃	H	H	H	H
S	O	2-SCF ₃	H	H	H	H
S	O	2-SO ₂ CF ₃	H	H	H	H
S	O	H	3-Cl	H	H	H

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Y	X	R ₁	R ₂	R ₃	R ₄	T
S	O	H	3-CO ₂ Et	H	H	H
S	O	H	3-CO ₂ H	H	H	H
S	O	H	3-CN	H	H	H
S	O	H	3-SCF ₃	H	H	H
S	O	H	H	4-Cl	H	H
S	O	H	H	4-SCF ₃	H	H
S	O	H	H	4-Cl	H	H
S	O	2-Br	H	4-Br	H	H
S	O	2-Cl	H	H	8-CN	H
S	O	2-Cl	H	H	8-CO ₂ Et	H
S	O	2-Cl	H	H	8-CO ₂ H	H
S	O	2-Cl	H	H	8-CF ₃	H
S	O	2-Cl	H	H	7-SO ₂ CH ₃	H
S	O	H	3-CONMe ₂	H	H	H
S	O	2-Cl	H	H	7-OCH ₃	H
S	O		H	H	H	H
S	O	2-SO ₂ CH ₃	H	H	H	H
S	O	2-CH ₂ CH=CH ₂	H	4-CH ₂ CH=CH ₂	H	H
S	O	H	3-N(CH ₃) ₂	H	H	H
S	O	H	H	4-Cl	7-S-C ₆ H ₅	H
S	O	2-CHCO ₂	H	H	H	H
S	O	2-Cl	H	4-SCH ₂ CO ₂ H	H	H
S	O	2-COC ₃	H	H	7-OCH ₃	H
S	O	H	H	4-CO-C ₆ H ₅	7-OCH ₃	H
S	NH	2-Cl	H	4-Cl	H	H
S	NH	H	3-N(CH ₃) ₂	H	H	H
S	NH	2-SCH ₃	H	4-SCH ₃	H	H
S	O	H	H	H	H	H
S	NH	H	H	H	H	H
S	O	2-COCH ₃	H	H	7-OCH ₃	H
S	O	H	H	4-COC ₆ H ₅	7-OCH ₃	H

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Y	X	R ₁	R ₂	R ₃	R ₄	T
S	NH.HCl	H	H	H	H	H
S	O	H	H	H	H	H
O	O	H	H	H	H	H
O	NH	H	H	H	H	H
O	S	H	H	H	H	H
O	NH.HCl	H	H	H	H	H
Se	O	H	H	H	H	H
Se	NH	H	H	H	H	H
Se	S	H	H	H	H	H
NH	NH.HCl	H	H	H	H	H
NH	S	H	H	H	H	H
O	O	4-Cl	H	H	H	H
O	O	4-Cl	H	7-OMe	H	H
O	O	4-Me	H	H	H	H
O	O	H	2-Cl	H	H	H
O	O	4-Cl	2-S-pPAA*	H	H	H
Se	O	4-Cl	H	H	H	H
Se	O	4-Cl	H	7-OMe	H	H
Se	O	4-Me	H	H	H	H
Se	O	4-Cl	2-S-pPAA*	H	H	H
N—CH ₃	O	4-Cl	H	H	H	H
N—C ₆ H ₆	O	4-Cl	H	7-OMe	H	H
N—H	O	4-Cl	2-S-pPAA*	H	H	H
S	O	4-Cl	H	H	H	H
SO	O	H	H	H	H	H
SO ₂	O	H	H	H	H	H
SO ₂	O	4-Cl	H	H	H	H
N—Me	O	H	H	H	H	H
N—Me	O	4-Cl	H	H	H	H
N—Me	O	4-Cl	H	7-OMe	H	H
NCN	O	4-Cl	H	H	H	H
NH	O	4-Cl	H	H	H	H

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	Y	X	R ₁	R ₂	R ₃	R ₄	T
	NH	O	4-Cl	H	H	H	H
5	S	O	2-t-Bu	9-t-Bu	4-OMe	H	H
	S	O	2-t-Bu	7-t-Bu	4-F	H	H
10	S	O	2-t-Bu	7-t-Bu	4-Me	H	H
	S	O	2-t-Bu	7-t-Bu	4-SMe	H	H

*p-PAA = para-Phenylacetic acid

15 12. The use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of the Formula I, a compound that is a salt of a compound of the Formula I, or a pharmaceutical composition containing such a compound, in which, in Formula I, the variables are as defined as follows, X being in the 3-position:

	R ₁	R ₂	R ₃	R ₄	T
20	H	H	H	H	H
	2-Cl	H	H	H	H
25	H	H	6-Cl	H	H
	H	H	7-Cl	H	H
30	H	H	8-Cl	H	H
	H	H	9-Cl	H	H
	1-Cl	H	H	H	H
35	1-Cl	4-Cl	H	H	H
	2-Cl	4-Cl	H	H	1-Cl
40	2-N(Me) ₂	H	H	H	H
	2-SMe	H	H	H	H
	2-S-pPAA	H	H	H	H
45	2-C(O)CH ₃	H	H	H	H
	2-OMe	H	H	H	H
50	H	H	H	7-CH ₂ CO ₂ H	H
	H	H	H	8-CH ₂ COOH	H
	H	2-SO ₃ H	H	H	H
55	2-N(Me) ₂	H	H	H	H
	2-SMe	H	H	H	H
60	2-C(O)CH ₃	H	H	H	H
	2-OMe	H	H	H	7-I
	2-CH ₂ CO ₂ H	H	H	H	H


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R ₁	R ₂	R ₃	R ₄	T
2-CH(CH ₃)CO ₂ H	H	H	H	H
4-CH ₂ COOH	H	H	H	H
4-CH(CH ₃)CO ₂ H	H	H	H	H
H	H	7-OH	6-propyl	H
4-Cl	H	H	H	H
4-F	H	H	H	H
4-F	H	7-Cl	H	H
4-Et	H	H	H	H
4-Et	H	7-OMe	H	H
4-Et	H	7-Cl	H	H
4-Cl	H	7-OMe	H	H
4-OMe	H	7-Cl	H	H
4-Cl	H	6-Cl	H	H
4-Cl	H	8-Cl	H	H
4-Cl	H	9-Cl	H	H
4-Cl	H	6-OMe	H	H
4-Cl	H	8-OMe	H	H
4-Cl	H	9-Et	H	H
4-Cl	H	6-Et	H	H
4-Cl	H	7-Et	H	H
4-Cl	H	8-Et	H	H
4-Cl	1-Et	H	H	H
4-Cl	2-Et	H	H	H
4-Cl	1-CH ₂ COOH	H	H	H
4-Cl	2-CH ₂ COOH	H	H	H
4-OH	2-OMe	7-OMe	H	H
4-OH	H	H	H	H
4-Me	1-OMe	2-OMe	H	H
4-Cl	H	6-CH ₂ COOH	H	H
4-Cl	H	7-CH ₂ COOH	H	H
4-Cl	H	8-CH ₂ COOH	H	H

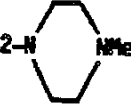
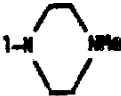


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R ₁	R ₂	R ₃	R ₄	T
4-Cl	2-N(Me) ₂	H	H	H
4-Cl	1-N(Me) ₂	H	H	H
4-Cl	2-N(Me) ₂	7-OMe	H	H
4-Cl	2-N(Me) ₂	7-Cl	H	H
4-Cl	2-SMe	H	H	H
4-Cl	2-SCH ₂ COOH	H	H	H
4-Cl	2-S-pPAA	H	H	H
4-Cl	1-S-pPAA	H	H	H
4-Cl	2-S-pPAA	7-OMe	H	H
4-Cl	2-SO ₃ H	H	H	H
4-Cl	2-OMe	H	H	H
4-Cl	2-OMe	7-Cl	H	H
4-Cl	H	7F	H	H
4-OMe	H	7-OMe	H	H
4-OMe	H	7-Me	H	H
4-OMe	2-SMe	H	H	H
4-SMe	H	H	H	H
4-Br	H	H	H	H
4-I	H	H	H	H
4-Br	H	7-OMe	H	H
4-I	H	7-OMe	H	H
4-Br	2-Me	H	H	H
4-I	2-Me	H	H	H
4-Cl	H	7/8-(CH ₂) ₄ —		H
4-Cl	H	7/8-(CH ₂) ₃ —		H
4-Br	2-OMe	7-OMe	H	H
7-F	H	H	H	H
7-NH ₂	H	H	H	H
2-Me	7-N(Me) ₂	H	H	H
7-N(Me) ₂	H	H	H	H
1-CO ₂ H	4-OH	7-NMe ₂	H	H

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R ₁	R ₂	R ₃	R ₄	T
1-Cl	2-Cl	4-Cl	H	7-Cl
1-Me	7-Me	H	H	4-Cl
2-Me	7-Me	H	H	4-Cl
2-Me	H	H	H	4-Cl
7-Me	H	H	H	4-Cl
9-OMe	H	H	H	H
2-OMe	H	H	H	7-F
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	7-Me	H	H
1-Me	7-Me	H	H	H
2-Me	7-Me	H	H	H
2-Cl	4-Cl	H	H	7-F
1-Cl	4-Cl	H	H	7-F
2-OMe	7-SMe	H	H	H
H	H	H	H	4-CF ₃
2-CF ₃	H	H	H	4-CF ₃
4-COMe	H	H	H	H
2-OEt	H	H	H	4-Cl
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
9-OMe	H	H	H	H
2-OMe	H	H	H	H
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	4-Me	H	H
4-OMe	H	H	H	H
1-OMe	7-OMe	H	H	4-Br
1-OMe	7-OMe	2-Cl	H	4-Cl
1-OMe	7-OMe	H	H	4-Cl
	7-OMe	H	H	H

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R ₁	R ₂	R ₃	R ₄	T
	7-OMe	H	H	4-Br
2-OMe	4-OH	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
		H	H	H
4-COMe	H	H	H	H
2-NHPr	4-NHPr	H	H	H
2-OMe	4-CN	7-OMe	H	H
2-OMe		7-OMe	H	H
2-OMe	7-OMe	H	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-NHPr	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
2-NHPr	4-NHPr	7-OMe	H	H
2-OMe	4-NH ₂	7-OMe	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-OMe	4-Cl	7-OMe	H	H
1-OMe	4-Br	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-OMe	4-CN	7-OMe	H	H
2-OMe	4-NHCH ₂ CO ₂ R*	7-OMe	H	H
2-OMe	4-S-7-Bu	7-OMe	H	H
2-OMe	4-CH ₂ CO ₂ R*	7-OMe	H	H
2-OMe	4-SO ₂ Me	7-OMe	H	H
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
2-OMe	7-Me	H	H	4-Br

	R ₁	R ₂	R ₃	R ₄	T
	2-OMe	7-CF ₃	H	H	4-Br
5	2-OMe	7-F	H	H	4-Br
	2-OMe	7-Cl	H	H	4-Br
10	2-OMe	7-Br	H	H	4-Br
	2-OMe	7-NMe ₂	H	H	4-Br
	2-OMe	7-SMe	H	H	4-Br
15	2-OMe	7-SO ₂ Me	H	H	4-Br
	2-OMe	7-Ph	H	H	4-Br
20	1-Me	H	H	H	4-Br
	2-Me	H	H	H	H
	2-OEt	H	H	H	H
25	7-Cl	H	H	H	H
	9-Cl	H	H	H	H
30	7-F	H	H	H	H
	7-Me	H	H	H	H
	7-OMe	H	H	H	H
35	2-Cl	H	H	H	4-Cl
	1-Me	7-Me	H	H	4-Cl
40	1-Me	7-Me	H	H	H
	2-OMe	7-OEt	H	H	H
	2-NH ₂	H	H	H	H
45	7-OH	H	H	H	H

* pPAA = para-Phenylacetic Acid

50 and in which R is H or C₁ to C₄ alkyl.

13. The use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of the Formula I, a compound that is a salt of a compound of the Formula I, or a pharmaceutical composition containing such a compound, in which, in Formula I, the variables are as defined as follows, X being in the 3-position:

55

60

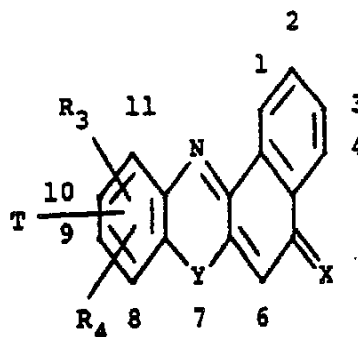
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Y	X	R ₁	R ₂	R ₃	R ₄	T
S	O	2-OMe	7-OMe	H	H	H
S	O	1-OMe	7-OMe	H	H	H
S	O	2-OMe	7-OMe	H	H	1-Br
S	O	1-OMe	7-OMe	H	H	2-Br
S	O	1-OMe	7-OMe	H	H	4-Br
S	O	1-OMe	7-OMe	H	H	2-Cl
S	O	1-OMe	7-OMe	H	H	4-Cl
S	O	2-OMe	7-OMe	H	H	1-Cl
S	O	2-OMe	7-OMe	H	H	4-Cl
S	O	2-OEt	7-OEt	H	H	1-Br
S	O	2-OEt	7-OEt	H	H	4-Br
S	O	2-OEt	7-OEt	H	H	1-Cl
S	O	2-OEt	7-OEt	H	H	4-Cl
S	O	2-OMe	7-OMe	8-OMe	H	1-Br
S	O	2-OMe	7-OMe	8-OMe	H	4-Br
S	O	2-OMe	7-OMe	H	H	4-F
S	O	2-OMe	7-OMe	H	H	4-CF ₃
S	O	2-OMe	7-OEt	H	H	4-Br
S	O	2-OMe	7-OEt	H	H	4-Cl
S	O	2-OMe	7-OEt	H	H	4-F
S	O	2-OMe	7-OEt	H	H	4-CF ₃
S	O	2-OEt	7-OMe	H	H	4-Br
S	O	2-OEt	7-OMe	H	H	4-Cl
S	O	2-OEt	7-OMe	H	H	4-F
S	O	2-OEt	7-OMe	H	H	4-CF ₃
S	O	2-OMe	7-OMe	H	H	4-Br

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14. The use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of the Formula I, a compound that is a salt of a compound of the Formula II:



where the substituents are:

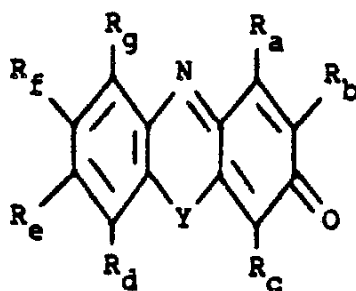
	Y	X	R ₃	R ₄	T
20	O	O	H	H	H
	S	O	H	H	H
25	SO	O	H	H	H
	SO ₂	O	H	H	H
	SO	O	H	H	6-Cl
30	S	O	6-COCH ₃	H	H
	S	O	6-CH ₃	H	H
35	SO ₂	O	6-OH	H	H
	SO ₂	O	6-OMe	H	H
	S	O	9-OMe	H	H
40	S	O	6-OH	H	H
	S	O	6-OMe	H	H
45	S	O	6-NHCOMe	H	H
	S	O	6-NHPh	H	H
	S	O	H	H	6-Br
50	S	O	6-NHMe	H	H
	S	O	6-NH-t-Bu	H	H
55	S	O	6-NH-COMe	H	9-Cl
	S	O	6-NH-COMe	9-Ome	H
	S	O	6-NHPh-p-Br	H	9-Cl
60	O	O	H	H	6-Cl
	O	O	H	H	6-Br
65	O	O	9-OMe	H	6-Br

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	Y	X	R ₃	R ₄	T
5	O	O	9-OMe	6-NHPr	H
	S	O	6-CF ₃	H	H
	S	O	6-S-n-Bu	H	H
10	S	O	6-OMe	H	9-Cl
	S	O	9-OMe	H	6-Cl
	S	O	6-OMe	9-OMe	H
15	S	O	6-Cl	9-Me	11-Br
	S	O	6-NHPh	9-Me	11-Br
20	S	O	6-Me	H	H
	O	NH	9-NMe ₂	10-Me	H
	O	NH	9-N(Et) ₂	H	H
25	S	O	6-Cl	H	H

15. A use as claimed in any one of Claims 1 to 14, applied to treatment of (1) pulmonary conditions, (2) inflammation, (3) allergies, (4) pain, (5) cardiovascular conditions or (6) skin conditions.

16. The compounds of the Formula:



in which the substituents are:

	Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
45	S	H	SCH ₃	H	H	H	H	H
	S	H	H	SCF ₃	H	H	H	H
50	S	H	H	CHO	H	H	H	H
	S	H	H	COCF ₃	H	H	H	H
55	S	H	H	H	H	SCH ₃	H	H
	S	H	H	H	H	CO ₂ CH ₃	H	H
	S	H	H	H	H	CO ₂ H	H	H
60	S	H	H	H	H	CHO	H	H
	S	H	H	H	H	CONH ₂	H	H
65	S	H	H	H	H	CH ₂ OH	H	H

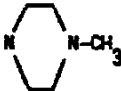
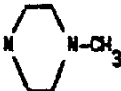
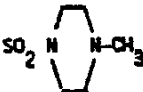

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Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	H	H	Cl	H	CO ₂ Me	H	H
S	H	H	Cl	H	CO ₂ H	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	CONH ₂	H	H
S	H	H	Cl	H	CH ₂ OH	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OE _t	H	H	CH ₃	H	H
S	CH ₃	H	Cl	H	CH ₃	H	H
S	H	CH ₃	Cl	H	CH ₃	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OE _t	Br	H	OE _t	H	H
S	H	OE _t	Cl	H	OE _t	H	H
S	H	OMe	Cl	H	OE _t	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
S	H	OMe	Br	H	Me	H	H
S	H	H	CHO	H	H	H	H
S	H	H	COCF ₃	H	H	H	H
S	H	H	H	H	SCH ₃	H	H
S	H	H	H	H	OCH ₃	H	H
S	H	H	H	H	CO ₂ CH ₃	H	H
S	H	H	H	H	CO ₂ H	H	H
S	H	H	H	H	CN	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	CONH ₂	H	H
S	H	H	H	H	CH ₂ OH	H	H
S	H	H	H	H	CF ₃	H	H
S	CH ₃	H	Cl	H	H	H	H
S	H	CH ₃	Cl	H	H	H	H


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Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	H	H	Cl	H	F	H	H
S	H	Cl	Cl	H	F	H	H
S	H	CH ₃	H	H	F	H	H
S	CH ₃	H	H	H	F	H	H
S	H	H	Cl	H	OMe	H	H
S	H	H	Cl	H	CF ₃	H	H
S	H	H	Cl	H	CO ₂ Me	H	H
S	H	H	Cl	H	CO ₂ H	H	H
S	H	H	Cl	H	CN	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	CONH ₂	H	H
S	H	H	Cl	H	CH ₂ OH	H	H
S	H	H	OCH ₃	H	Cl	H	H
S	H	H	CF ₃	H	Cl	H	H
S	H	OEt	Cl	H	H	H	H
S	H	OiPr	H	H	H	H	H
S	OMe	H	Cl	H	H	H	H
S	OEt	H	Cl	H	H	H	H
S	H	OiPr	Cl	H	H	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	F	H	H
S	H	OCH ₃	Cl	H	H	H	H
S	H	OEt	H	H	CH ₃	H	H
S	H	OEt	Cl	H	F	H	H
S	H	OEt	Cl	H	CH ₃	H	H
S	H	H	Cl	H	CH ₃	H	H
S	H	CH ₃	Cl	H	H	H	H
S	H	CH ₃	Br	H	H	H	H
S	CH ₃	H	H	H	CH ₃	H	H
S	H	CH ₃	H	H	CH ₃	H	H
S	CH ₃	H	Cl	H	CH ₃	H	H
S	H	CH ₃	Cl	H	CH ₃	H	H

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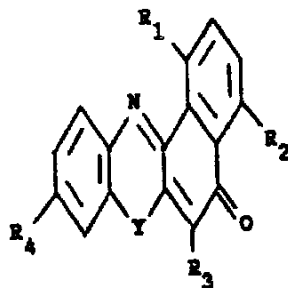
Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	Cl	H	Cl	H	F	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
O	H	H	Cl	H	H	H	H
S	H	OMe	Br	H	Me	H	H
SO ₂	H	H	OH	H	H	H	H
SO ₂	H	OMe	OH	H	OMe	H	H
SO ₂	OMe	OMe	Me	H	H	H	H
SO ₂	H	H	OMe	H	H	H	H
SO ₂	H	OMe	OMe	H	OMe	H	H
S	H	H	H	H	H	H	OCH ₃
S	H	OCH ₃	H	H	F	H	H
S	H	OCH ₃ H	OCH ₃	H	H	H	H
S	OCH ₃	OCH ₃	Me	H	H	H	H
S	H	H	COCH ₃	H	H	H	H
S	OCH ₃	H	Br	H	OCH ₃	H	H
S	OCH ₃	Cl	Cl	H	OCH ₃	H	H
S	OCH ₃	H	Cl	H	OCH ₃ H	H	H
S	H		H	H	OCH ₃	H	H
S	H		Br	H	OCH ₃	H	H
SO ₂	H	OCH ₃	OH	H	OCH ₃	H	H
SO ₂	NHPr	H	NHPr	H	H	H	H
		H		H	H	H	H

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Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
SO ₂	H	OCH ₃		H	OCH ₃	H	H
SO ₂	H	OCH ₃	Br	H	OCH ₃	H	H
S	NHPR	H	NHPr	H	H	H	H
S	NHPr	H	NHPr	H	OCH ₃	H	H
S	H	NHPr	NHPr	H	H	H	H
S	H	NHPr	NHPr	H	OCH ₃	H	H
S	H	OCH ₃	NH ₂	H	OCH ₃	H	H
S	H	OCH ₃	NHPr	H	OCH ₃	H	H
SO ₂	H	OCH ₃	NHPr	H	OCH ₃	H	H
O	OCH ₃	H	Cl	H	OCH ₃	H	H
O	OCH ₃	H	Br	H	OCH ₃	H	H
O	NHPr	H	NHPr	H	H	H	H
SO ₂	H	OCH ₃	CN	H	OCH ₃	H	H
SO ₂	H	OCH ₃	NHCH ₂ CO ₂ R*	H	OCH ₃	H	H
SO ₂	H	OCH ₃	S-N-Bu	H	OCH ₃	H	H
SO ₂	H	OCH ₃	CH ₂ CO ₂ R*	H	OCH ₃	H	H
SO ₂	H	OCH ₃	SO ₂ CH ₃	H	OCH ₃	H	H
S	H	S-n-Bu	H	H	H	H	H
S	H	H	S-n-Bu	H	H	H	H
S	H	CH ₃	S-n-Bu	H	H	H	H
S	H	OMe	Br	H	CF ₃	H	H
S	H	OMe	Br	H	F	H	H
S	H	OMe	Br	H	Cl	H	H
S	H	OMe	Br	H	Br	H	H
S	H	OMe	Br	H	NMe ₂	H	H
S	H	OMe	Br	H	SMe	H	H
S	H	OMe	Br	H	SO ₂ Me	H	H
S	H	OMe	Br	H	Ph	H	H
S	H	H	H	Cl	OMe	H	H

and R is H or C₂ to C₄ alkyl.


17. The compounds of the Formula:



wherein the substituents are:

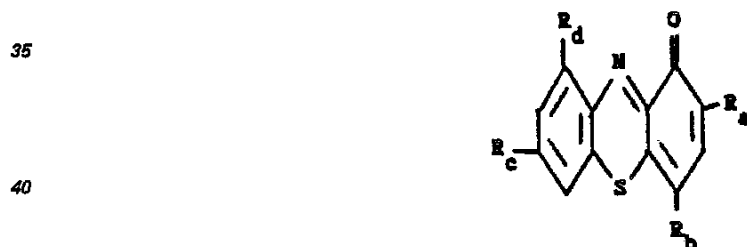
	Y	R ₁	R ₂	R ₃	R ₄
15	S	H	H	S-n-CH ₄ H ₉	H
	S	OH	H	CH ₃	H
20	S	OCH ₃	H	CH ₃	H
	S	H	H	F	H
25	S	H	H	CF ₃	H
	S	H	H	Cl	CF ₃
	S	H	H	Cl	SCH ₃
30	S	H	H	Br	Cl
	S	H	H	CH ₃	Br
35	S	H	H	F	Br
	S	H	H	COCH ₃	Cl
	S	H	H	CF ₃	CH ₃
40	S	H	H	SC ₄ H ₉	CH ₃
	S	H	H	CF ₃	Cl
45	S	H	H	Cl	CH ₂ COOR
	S	H	H	Cl	CH(Me)CO ₂ R
	S	H	H	Cl	COCH ₃
50	S	H	H	H	Cl
	S	H	H	H	Br
55	S	H	H	H	F
	S	H	H	H	CF ₃
	S	H	H	H	CH ₃
60	S	H	H	H	CH ₂ OH
	S	H	H	H	OCH ₃
65	S	H	H	H	SCH ₃

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	Y	R ₁	R ₂	R ₃	R ₄
	S	H	H	H	COOR
5	S	H	H	H	CH ₂ CO ₂ R
	S	H	H	H	CH(Me)CO ₂ R
10	SO ₂	H	H	NHPr	H
	SO ₂	H	H		H
15	SO ₂	H	H	NH ₂	H
	SO ₂	H	H	NHPr	OCH ₃
20	S	-1,4-dihydro-		H	H
	S	H	H	NHPr	OCH ₃
	O	H	H	Cl	H
25	O	H	H	Br	H
	O	H	H	Br	OCH ₃
30	O	H	H	NHPr	OCH ₃

and wherein R is H or C₁ to C₄ alkyl.

18. The compounds of the formula:



III

where the substituents are:

45

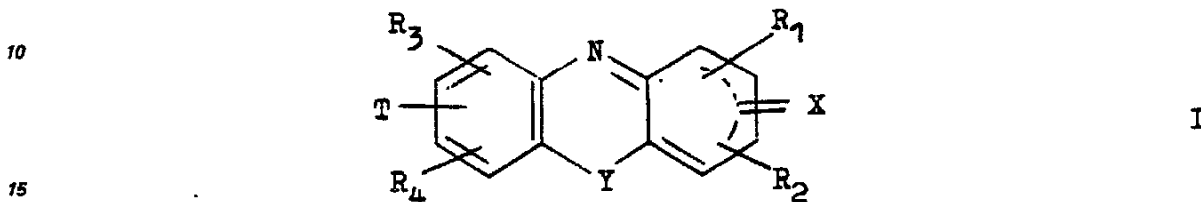
	R _a	R _b	R _c	R _d
	t-Bu	t-Bu	H	H
50	t-Bu	t-Bu	F	H
	t-Bu	t-Bu	Me	H
	t-Bu	t-Bu	SMe	H
55	t-Bu	t-Bu	H	OMe

19. The compounds 2-S-glutathionyl-3H-phenothiazin-3-one and 4-chloro-2-S-glutathionyl-phenothiazin-3-one.

20. The use claimed in Claim 1 of the manufacture of a medicament that additionally contains a second active ingredient that is a non-steroidal antiinflammatory agent; a peripheral analgesic agent; a cyclooxygenase inhibitor; a leukotriene antagonist, an antihistaminic agent; a prostaglandin antagonist; or a thromboxane antagonist, in which the weight ratio of the Formula I compound to the second active ingredient ranges from 10:1 to 1:10.

Patentansprüche

1. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung der Formel I ist, oder einer eine solche Verbindung enthaltenden pharmazeutischen Zusammensetzung:



worin

- 20 X in der 1- oder 3-Stellung ist und O, S oder NR ist;
 R H, verzweigtes oder lineares C₁₋₆-Alkyl, CN oder Phenyl ist;
 Y O, Se, S, SO, SO₂ oder NR ist; und die gestrichelte Linie eine Doppelbindung zwischen der 1- und 2- oder 2- und 3-Stellung darstellt;
 jedes von R₁, R₂, R₃ und R₄ unabhängig von den anderen
- 25 (1) Wasserstoff,
 (2) 1-6-Alkyl,
 (3) 2-6-Alkenyl,
 (4) —(CH₂)_nM ist,
 worin n 0 oder eine ganze Zahl von 1 bis 6 ist und M
- 30 (a) OR₅,
 (b) Halogen,
 (c) CF₃,
 (d) SR₅, worin R₅ H; C₁₋₆-Alkyl; Benzyl; Phenyl oder substituiertes Phenyl, worin die Substituenten C₁₋₃-Alkyl, Halogen, CN, CF₃, COOR₆, CN₂COOR₆, (CH₂)_nNR₈R₉ worin n 0, 1 oder 2 ist, C₁₋₃-Alkoxy, OH oder C₁₋₆-Halogenalkyl; sind; —(CH₂)_mCOOR₆, worin m 0 oder eine ganze Zahl von 1 bis 6 ist und R₆ H, Phenyl oder C₁₋₆-Alkyl; CN, Formyl, CF₃ oder CH₂—R₁₂, worin R₁₂ C₁₋₆-Alkyl, Phenyl oder Dimethylamino ist; ist;
 (e) Phenyl oder substituiertes Phenyl, wie oben für R₅ definiert;
 (f) COOR₆;



worin R₁₅ H, (CH₂)_n COOR₆, worin n 0 oder eine ganze Zahl von 1 bis 4 ist, C₁₋₆-Alkyl, CF₃, Phenyl oder substituiertes Phenyl, wie oben für R₅ definiert;

- 45 (h) Tetrazol;



50 worin R₇ C₁₋₆-Alkyl, Benzyl oder Phenyl ist;

(j) —NR₈R₉ worin R₈ und R₉ unabhängig aus H, Phenyl oder substituiertem Phenyl, wie oben für R₅ definiert, oder C₁₋₄-Alkyl, C₁₋₄-Alkylaminoalkyl ausgewählt sind, oder über das N unter Bildung eines 4-Methylpiperazinylrestes verbunden sein können;

(k) —NHSO₂R₁₀, worin R₁₀ OH, C₁₋₆-Alkyl, C₁₋₆-Alkoxy, Phenyl oder CF₃ ist;

55



60 (m) —SOR₁₁, worin R₁₁ C₁₋₆-Alkyl, Phenyl oder substituiertes Phenyl, wie oben für R₅ definiert, (CH₂)_mCOOR₆, worin m 1 bis 6 ist, CN, Formyl oder CF₃ ist;

(n) —CONR₈R₉;

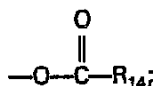
(o) —SO₂NR₈R₉;

(p) —SO₂R₁₃, worin R₁₃ OH, H, C₁₋₆-Alkyl, Phenyl oder substituiertes Phenyl, wie oben für R₅ definiert,

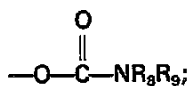
65 (CH₂)_mCOOR₆, worin m 1 bis 6 ist, CN oder CF₃ ist;

(q) NO₂;

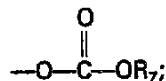
(r)



(s)



(t)



(u) —CN; oder

(v) NR₁₅R₁₆ worin R₁₅ und R₁₆ so sind, daß HNR₁₅R₁₆ eine essentielle Aminosäure darstellt; oder jeweils zwei von R₁, R₂, R₃ und R₄ unter Bildung eines vierten gesättigten oder ungesättigten C₅—C₆-Rings zusammengekommen werden; und T H, Halogen oder CF₃ ist.

2. Verwendung, wie in Anspruch 1 beansprucht, worin in Formel I X in der 1-Stellung ist.

3. Verwendung, wie in Anspruch 2 beansprucht, worin X O oder NR ist.

4. Verwendung, wie in Anspruch 3 beansprucht, worin in Formel I Y S, SO, SO₂, NR oder O ist und in der Struktureinheit (CH₂)_n M n 0 oder 1 ist.

5. Verwendung, wie in Anspruch 4 beansprucht, worin in Formel I X O ist und Y S ist.

6. Verwendung, wie in Anspruch 1 beansprucht, worin in Formel I X in der 3-Stellung ist.

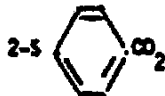
7. Verwendung, wie in Anspruch 6 beansprucht, worin X O oder NR ist.

8. Verwendung, wie in Anspruch 7 beansprucht, worin in Formel I Y S, SO, SO₂, NR oder O ist und in der Struktureinheit (CH₂)_n M n 0 oder 1 ist.

9. Verwendung, wie in Anspruch 8 beansprucht, worin Y S oder O ist.

10. Verwendung, wie in Anspruch 9 beansprucht, worin X O ist und Y S ist.

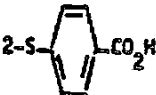
11. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung der Formel I ist, oder einer eine solche Verbindung enthaltenden pharmazeutischen Zusammensetzung, worin in der Formel I die Variablen wie nachstehend definiert sind und X in der 1-Stellung ist.

	Y	X	R ₁	R ₂	R ₃	R ₄	T
35	O	O	2-t-Bu	8-t-Bu	4-t-Bu	6-t-Bu	H
	O	O	2-t-Bu	H	4-Me	H	H
40	S	S	2-t-Bu	4-t-Bu	H	H	H
	N—CH ₃ , S, O, Se, SO oder SO ₂	O	2-Cl	H	H	H	H
45	"	O	2-SCF ₃	H	H	H	H
50	"	O	2-S 	H	H	H	H
	S	O	2-t-Bu	4-t-Bu	H	H	H
55	N—CH ₃ , S, O, Se, SO oder SO ₂	O	2-CN	H	H	H	H
	"	O	H	3-CO ₂ Et	H	H	H
60	"	O	H	3-Cl	H	H	H
	"	O	H	H	4-Cl	H	H
65	"	O	H	H	4-SO ₂ CH ₃	H	H

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Y	X	R ₁	R ₂	R ₃	R ₄	T
SO ₂	O	2-Cl	H	4-Cl	H	H
"	NH	2-Cl	H	4-Cl	H	H
"	NH	H	H	H	H	H
N—CN	O	2-Cl	H	4-Cl	H	H
S	O	H	H	H	H	H
S	O	2-Cl	3-Cl	4-Cl	7-Cl	9-Cl
S	O	2-Br	3-Br	4-Br	7-Br	9-Br
S	O	H	H	H	7-SO ₂ CH ₃	H
S	O	2-Cl	H	4-SO ₂ CH ₃	H	H
S	O	2-F	H	4-Cl	H	H
S	O	2-Br	H	H	H	H
S	O	2-CF ₃	H	H	H	H
S	O	2-SCF ₃	H	H	H	H
S	O	2-SO ₂ CF ₃	H	H	H	H
S	O	H	3-Cl	H	H	H
S	O	H	3-CO ₂ Et	H	H	H
S	O	H	3-CO ₂ H	H	H	H
S	O	H	3-CN	H	H	H
S	O	H	3-SCF ₃	H	H	H
S	O	H	H	4-Cl	H	H
S	O	H	H	4-SCF ₃	H	H
S	O	H	H	4-Cl	H	H
S	O	2-Br	H	4-Br	H	H
S	O	2-Cl	H	H	8-CN	H
S	O	2-Cl	H	H	8-CO ₂ Et	H
S	O	2-Cl	H	H	8-CO ₂ H	H
S	O	2-Cl	H	H	8-CF ₃	H
S	O	2-Cl	H	H	7-SO ₂ CH ₃	H
S	O	H	3-CONMe ₂	H	H	H
S	O	2-Cl	H	H	7-OCH ₃	H

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Y	X	R ₁	R ₂	R ₃	R ₄	T
S	O		H	H	H	H
S	O	2-SO ₂ CH ₃	H	H	H	H
S	O	2-CH ₂ CH=CH ₂	H	4-CH ₂ CH=CH ₂	H	H
S	O	H	3-N(CH ₃) ₂	H	H	H
S	O	H	H	4-Cl	7-S-C ₆ H ₆	H
S	O	2-CHCO ₂	H	H	H	H
S	O	2-Cl	H	4-SCH ₂ CO ₂ H	H	H
S	O	2-COC ₃	H	H	7-OCH ₃	H
S	O	H	H	4-CO-C ₆ H ₆	7-OCH ₃	H
S	NH	2-Cl	H	4-Cl	H	H
S	NH	H	3-N(CH ₃) ₂	H	H	H
S	NH	2-SCH ₃	H	4-SCH ₃	H	H
S	O	H	H	H	H	H
S	NH	H	H	H	H	H
S	O	2-COCH ₃	H	H	7-OCH ₃	H
S	O	H	H	4-COC ₆ H ₅	7-OCH ₃	H
S	NH.HCl	H	H	H	H	H
S	O	H	H	H	H	H
O	O	H	H	H	H	H
O	NH	H	H	H	H	H
O	S	H	H	H	H	H
O	NH.HCl	H	H	H	H	H
Se	O	H	H	H	H	H
Se	NH	H	H	H	H	H
Se	S	H	H	H	H	H
NH	NH.HCl	H	H	H	H	H
NH	S	H	H	H	H	H
O	O	4-Cl	H	H	H	H
O	O	4-Cl	H	7-OMe	H	H
O	O	4-Me	H	H	H	H

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	Y	X	R ₁	R ₂	R ₃	R ₄	T
	O	O	H	2-Cl	H	H	H
5	O	O	4-Cl	2-S-pPAA*	H	H	H
	Se	O	4-Cl	H	H	H	H
10	Se	O	4-Cl	H	7-OMe	H	H
	Se	O	4-Me	H	H	H	H
	Se	O	4-Cl	2-S-pPAA*	H	H	H
15	N-CH ₃	O	4-Cl	H	H	H	H
	N-C ₆ H ₅	O	4-Cl	H	7-OMe	H	H
20	N-H	O	4-Cl	2-S-pPAA*	H	H	H
	S	O	4-Cl	H	H	H	H
	SO	O	H	H	H	H	H
25	SO ₂	O	H	H	H	H	H
	SO ₂	O	4-Cl	H	H	H	H
30	N-Me	O	H	H	H	H	H
	N-Me	O	4-Cl	H	H	H	H
	N-Me	O	4-Cl	H	7-OMe	H	H
35	NCN	O	4-Cl	H	H	H	H
	NH	O	4-Cl	H	H	H	H
40	NH	O	4-Cl	H	H	H	H
	S	O	2-t-Bu	9-t-Bu	4-OMe	H	H
	S	O	2-t-Bu	7-t-Bu	4-F	H	H
45	S	O	2-t-Bu	7-t-Bu	4-Me	H	H
	S	O	2-t-Bu	7-t-Bu	4-SMe	H	H

50 *pPAA = Paraphenylelessigsäure

12. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder
 -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung
 der Formel I ist, oder einer eine solche Verbindung enthaltenden pharmazeutischen Zusammensetzung,
 55 worin in Formel I die Variablen wie nachstehend definiert sind und X in der 3-Stellung ist.

	R ₁	R ₂	R ₃	R ₄	T
60	H	H	H	H	H
	2-Cl	H	H	H	H
	H	H	6-Cl	H	H
65	H	H	7-Cl	H	H

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R ₁	R ₂	R ₃	R ₄	T
H	H	8-Cl	H	H
H	H	9-Cl	H	H
1-Cl	H	H	H	H
1-Cl	4-Cl	H	H	H
2-Cl	4-Cl	H	H	1-Cl
2-N(Me) ₂	H	H	H	H
2-SMe	H	H	H	H
2-S-pPAA	H	H	H	H
2-C(O)CH ₃	H	H	H	H
2-OMe	H	H	H	H
H	H	H	7-CH ₂ CO ₂ H	H
H	H	H	8-CH ₂ COOH	H
H	2-SO ₃ H	H	H	H
2-N(Me) ₂	H	H	H	H
2-SMe	H	H	H	H
2-C(O)CH ₃	H	H	H	H
2-OMe	H	H	H	7-I
2-CH ₂ CO ₂ H	H	H	H	H
2-CH(CH ₃)CO ₂ H	H	H	H	H
4-CH ₂ COOH	H	H	H	H
4-CH(CH ₃)CO ₂ H	H	H	H	H
H	H	7-OH	6-propyl	H
4-Cl	H	H	H	H
4-F	H	H	H	H
4-F	H	7-Cl	H	H
4-Et	H	H	H	H
4-Et	H	7-OMe	H	H
4-Et	H	7-Cl	H	H
4-Cl	H	7-OMe	H	H
4-OMe	H	7-Cl	H	H
4-Cl	H	6-Cl	H	H
4-Cl	H	8-Cl	H	H

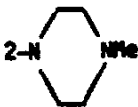
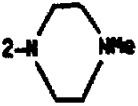
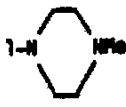
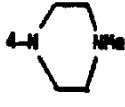
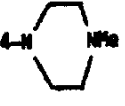
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R ₁	R ₂	R ₃	R ₄	T
4-Cl	H	9-Cl	H	H
4-Cl	H	6-OMe	H	H
4-Cl	H	8-OMe	H	H
4-Cl	H	9-Et	H	h
4-Cl	H	6-Et	H	H
4-Cl	H	7-Et	H	H
4-Cl	H	8-Et	H	H
4-Cl	1-Et	H	H	H
4-Cl	2-Et	H	H	H
4-Cl	1-CH ₂ COOH	H	H	H
4-Cl	2-CH ₂ COOH	H	H	H
4-OH	2-OMe	7-OMe	H	H
4-OH	H	H	H	H
4-Me	1-OMe	2-OMe	H	H
4-Cl	H	6-CH ₂ COOH	H	H
4-Cl	H	7-CH ₂ COOH	H	H
4-Cl	H	8-CH ₂ COOH	H	H
4-Cl	2-N(Me) ₂	H	H	H
4-Cl	1-N(Me) ₂	H	H	H
4-Cl	2-N(Me) ₂	7-OMe	H	H
4-Cl	2-N(Me) ₂	7-Cl	H	H
4-Cl	2-SMe	H	H	H
4-Cl	2-SCH ₂ COOH	H	H	H
4-Cl	2-S-pPAA	H	H	H
4-Cl	1-S-pPAA	H	H	H
4-Cl	2-S-pPAA	7-OMe	H	H
4-Cl	2-SO ₃ H	H	H	H
4-Cl	2-OMe	H	H	H
4-Cl	2-OMe	7-Cl	H	H
4-Cl	H	7F	H	H
4-OMe	H	7-OMe	H	H

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R ₁	R ₂	R ₃	R ₄	T
4-OMe	H	7-Me	H	H
4-OMe	2-SMe	H	H	H
4-SMe	H	H	H	H
4-Br	H	H	H	H
4-I	H	H	H	H
4-Br	H	7-OMe	H	H
4-I	H	7-OMe	H	H
4-Br	2-Me	H	H	H
4-I	2-Me	H	H	H
4-Cl	H	7/8-(CH ₂) ₄ —		H
4-Cl	H	7/8-(CH ₂) ₃ —		H
4-Br	2-OMe	7-OMe	H	H
7-F	H	H	H	H
7-NH ₂	H	H	H	H
2-Me	7-N(Me) ₂	H	H	H
7-N(Me) ₂	H	H	H	H
1-CO ₂ H	4-OH	7-NMe ₂	H	H
1-Cl	2-Cl	4-Cl	H	7-Cl
1-Me	7-Me	H	H	4-Cl
2-Me	7-Me	H	H	4-Cl
2-Me	H	H	H	4-Cl
7-Me	H	H	H	4-Cl
9-OMe	H	H	H	H
2-OMe	H	H	H	7-F
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	7-Me	H	H
1-Me	7-Me	H	H	H
2-Me	7-Me	H	H	H
2-Cl	4-Cl	H	H	7-F
1-Cl	4-Cl	H	H	7-F
2-OMe	7-SMe	H	H	H

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R ₁	R ₂	R ₃	R ₄	T
H	H	H	H	4-CF ₃
2-CF ₃	H	H	H	4-CF ₃
4-COMe	H	H	H	H
2-OEt	H	H	H	4-Cl
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
9-OMe	H	H	H	H
2-OMe	H	H	H	H
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	4-Me	H	H
4-OMe	H	H	H	H
1-OMe	7-OMe	H	H	4-Br
1-OMe	7-OMe	2-Cl	H	4-Cl
1-OMe	7-OMe	H	H	4-Cl
	7-OMe	H	H	H
	7-OMe	H	H	4-Br
2-OMe	4-OH	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
		H	H	H
4-COMe	H	H	H	H
2-NHPr	4-NHPr	H	H	H
2-OMe	4-CN	7-OMe	H	H
2-OMe		7-OMe	H	H
2-OMe	7-OMe	H	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H

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R ₁	R ₂	R ₃	R ₄	T
1-NHPr	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
2-NHPr	4-NHPr	7-OMe	H	H
2-OMe	4-NH ₂	7-OMe	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-OMe	4-Cl	7-OMe	H	H
1-OMe	4-Br	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-OMe	4-CN	7-OMe	H	H
2-OMe	4-NHCH ₂ CO ₂ R*	7-OMe	H	H
2-OMe	4-S-7-Bu	7-OMe	H	H
2-OMe	4-CH ₂ CO ₂ R*	7-OMe	H	H
2-OMe	4-SO ₂ Me	7-OMe	H	H
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
2-OMe	7-Me	H	H	4-Br
2-OMe	7-CF ₃	H	H	4-Br
2-OMe	7-F	H	H	4-Br
2-OMe	7-Cl	H	H	4-Br
2-OMe	7-Br	H	H	4-Br
2-OMe	7-NMe ₂	H	H	4-Br
2-OMe	7-SMe	H	H	4-Br
2-OMe	7-SO ₂ Me	H	H	4-Br
2-OMe	7-Ph	H	H	4-Br
1-Me	H	H	H	4-Br
2-Me	H	H	H	H
2-OEt	H	H	H	H
7-Cl	H	H	H	H
9-Cl	H	H	H	H
7-F	H	H	H	H
7-Me	H	H	H	H

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	R ₁	R ₂	R ₃	R ₄	T
	7-OMe	H	H	H	H
5	2-Cl	H	H	H	4-Cl
	1-Me	7-Me	H	H	4-Cl
10	1-Me	7-Me	H	H	H
	2-OMe	7-OEt	H	H	H
	2-NH ₂	H	H	H	H
15	7-OH	H	H	H	H

pPAA = Paraphenylelessigsäure und worin R H oder C₁—C₄-Alkyl ist.

20

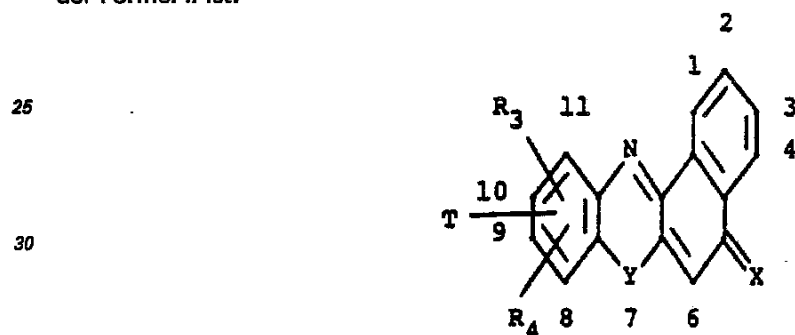
13. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung der Formel I ist, oder einer eine solche Verbindung enthaltenden pharmazeutischen Zusammensetzung, worin in Formel I die Variablen wie nachstehend definiert sind und X in der 3-Stellung ist:

	Y	X	R ₁	R ₂	R ₃	R ₄	T
30	S	O	2-OMe	7-OMe	H	H	H
	S	O	1-OMe	7-OMe	H	H	H
	S	O	2-OMe	7-OMe	H	H	1-Br
35	S	O	1-OMe	7-OMe	H	H	2-Br
	S	O	1-OMe	7-OMe	H	H	4-Br
40	S	O	1-OMe	7-OMe	H	H	2-Cl
	S	O	1-OMe	7-OMe	H	H	4-Cl
	S	O	2-OMe	7-OMe	H	H	1-Cl
45	S	O	2-OMe	7-OMe	H	H	4-Cl
	S	O	2-OEt	7-OEt	H	H	1-Br
	S	O	2-OEt	7-OEt	H	H	4-Br
50	S	O	2-OEt	7-OEt	H	H	1-Cl
	S	O	2-OEt	7-OEt	H	H	4-Cl
55	S	O	2-OMe	7-OMe	8-OMe	H	1-Br
	S	O	2-OMe	7-OMe	8-OMe	H	4-Br
	S	O	2-OMe	7-OMe	H	H	4-F
60	S	O	2-OMe	7-OMe	H	H	4-CF ₃
	S	O	2-OMe	7-OEt	H	H	4-Be
65	S	O	2-OMe	7-OEt	H	H	4-Cl

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	Y	X	R ₁	R ₂	R ₃	R ₄	T
5	S	O	2-OMe	7-OEt	H	H	4-F
	S	O	2-OMe	7-OEt	H	H	4-CF ₃
	S	O	2-OEt	7-OMe	H	H	4-Br
10	S	O	2-OEt	7-OMe	H	H	4-Cl
	S	O	2-OEt	7-OMe	H	H	4-F
15	S	O	2-OEt	7-OMe	H	H	4-CF ₃
	S	O	2-OMe	7-OMe	H	H	4-Br

14. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder
 20 -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung
 der Formel II ist:



35 worin die Substituenten wie folgt sind:

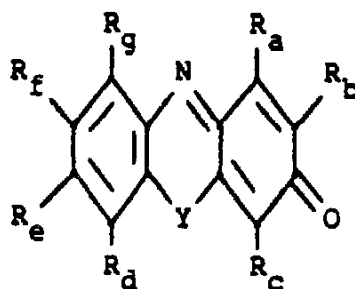
	Y	X	R ₃	R ₄	T
40	O	O	H	H	H
	S	O	H	H	H
	SO	O	H	H	H
45	SO ₂	O	H	H	H
	SO	O	H	H	6-Cl
50	S	O	6-COCH ₃	H	H
	S	O	6-CH ₃	H	H
	SO ₂	O	6-OH	H	H
55	SO ₂	O	6-OMe	H	H
	S	O	9-OMe	H	H
	S	O	6-OH	H	H
60	S	O	6-OMe	H	H
	S	O	6-NHCOMe	H	H
65	S	O	6-NHPh	H	H

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	Y	X	R ₃	R ₄	T
	S	O	H	H	6-Br
5	S	O	6-NHMe	H	H
	S	O	6-NH-t-Bu	H	H
10	S	O	6-NH-COMe	H	9-Cl
	S	O	6-NH-COMe	9-Ome	H
	S	O	6-NHPh-p-Br	H	9-Cl
15	O	O	H	H	6-Cl
	O	O	H	H	6-Br
20	O	O	9-OMe	H	6-Br
	O	O	9-OMe	6-NHPr	H
	S	O	6-CF ₃	H	H
25	S	O	6-S-n-Bu	H	H
	S	O	6-OMe	H	9-Cl
	S	O	9-OMe	H	6-Cl
30	S	O	6-OMe	9-OMe	H
	S	O	6-Cl	9-Me	11-Br
35	S	O	6-NHPh	9-Me	11-Br
	S	O	6-Me	H	H
40	O	NH	9-NMe ₂	10-Me	H
	O	NH	9-N(Et) ₂	H	H
	S	O	6-Cl	H	H

15. Verwendung, wie in einem der Ansprüche 1 bis 14 beansprucht, angewandt auf die Behandlung von (1) Lungenzuständen, (2) Entzündungen, (3) Allergien, (4) Schmerz, (5) cardiovaskuläre Zustände oder (6) Hautzustände.

16. Verbindungen der Formel



worin die Substituenten wie folgt sind:

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Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	H	SCH ₃	H	H	H	H	H
S	H	H	SCF ₃	H	H	H	H
S	H	H	CHO	H	H	H	H
S	H	H	COCF ₃	H	H	H	H
S	H	H	H	H	SCH ₃	H	H
S	H	H	H	H	CO ₂ CH ₃	H	H
S	H	H	H	H	CO ₂ H	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	CONH ₂	H	H
S	H	H	H	H	CH ₂ OH	H	H
S	H	H	Cl	H	CO ₂ Me	H	H
S	H	H	Cl	H	CO ₂ H	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	CONH ₂	H	H
S	H	H	Cl	H	CH ₂ OH	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	CH ₃	H	H
S	CH ₃	H	Cl	H	CH ₃	H	H
S	H	CH ₃	Cl	H	CH ₃	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
S	H	OMe	Br	H	Me	H	H
S	H	H	CHO	H	H	H	H
S	H	H	COCF ₃	H	H	H	H
S	H	H	H	H	SCH ₃	H	H
S	H	H	H	H	OCH ₃	H	H

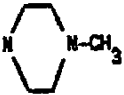
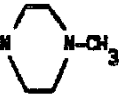
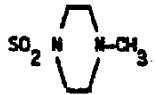

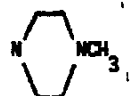
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Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	H	H	H	H	CO ₂ CH ₃	H	H
S	H	H	H	H	CO ₂ H	H	H
S	H	H	H	H	CN	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	CONH ₂	H	H
S	H	H	H	H	CH ₂ OH	H	H
S	H	H	H	H	CF ₃	H	H
S	CH ₃	H	Cl	H	H	H	H
S	H	CH ₃	Cl	H	H	H	H
S	H	H	Cl	H	F	H	H
S	H	Cl	Cl	H	F	H	H
S	H	CH ₃	H	H	F	H	H
S	CH ₃	H	H	H	F	H	H
S	H	H	Cl	H	OMe	H	H
S	H	H	Cl	H	CF ₃	H	H
S	H	H	Cl	H	CO ₂ Me	H	H
S	H	H	Cl	H	CO ₂ H	H	H
S	H	H	Cl	H	CN	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	CONH ₂	H	H
S	H	H	Cl	H	CH ₂ OH	H	H
S	H	H	OCH ₃	H	Cl	H	H
S	H	H	CF ₃	H	Cl	H	H
S	H	OEt	Cl	H	H	H	H
S	H	OiPr	H	H	H	H	H
S	OMe	H	Cl	H	H	H	H
S	OEt	H	Cl	H	H	H	H
S	H	OiPr	Cl	H	H	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	F	H	H

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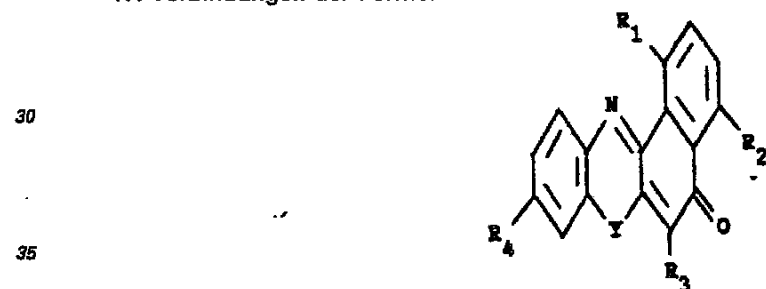
Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	H	OCH ₃	Cl	H	H	H	H
S	H	OEt	H	H	CH ₃	H	H
S	H	OEt	Cl	H	F	H	H
S	H	OEt	Cl	H	CH ₃	H	H
S	H	H	Cl	H	CH ₃	H	H
S	H	CH ₃	Cl	H	H	H	H
S	H	CH ₃	Br	H	H	H	H
S	CH ₃	H	H	H	CH ₃	H	H
S	H	CH ₃	H	H	CH ₃	H	H
S	CH ₃	H	Cl	H	CH ₃	H	H
S	H	CH ₃	Cl	H	CH ₃	H	H
S	Cl	H	Cl	H	F	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
O	H	H	Cl	H	H	H	H
S	H	OMe	Br	H	Me	H	H
SO ₂	H	H	OH	H	H	H	H
SO ₂	H	OMe	OH	H	OMe	H	H
SO ₂	OMe	OMe	Me	H	H	H	H
SO ₂	H	H	OMe	H	H	H	H
SO ₂	H	OMe	OMe	H	OMe	H	H
S	H	H	H	H	H	H	OCH ₃
S	H	OCH ₃	H	H	F	H	H
S	H	OCH ₃ H	OCH ₃	H	H	H	H
S	OCH ₃	OCH ₃	Me	H	H	H	H
S	H	H	COCH ₃	H	H	H	H

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Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	OCH ₃	H	Br	H	OCH ₃	H	H
S	OCH ₃	Cl	Cl	H	OCH ₃	H	H
S	OCH ₃	H	Cl	H	OCH ₃ H	H	H
S	H		H	H	OCH ₃	H	H
S	H		Br	H	OCH ₃	H	H
SO ₂	H	OCH ₃	OH	H	OCH ₃	H	H
SO ₂	NHPr	H	NHPr	H	H	H	H
		H		H	H	H	H
SO ₂	H	OCH ₃		H	OCH ₃	H	H
SO ₂	H	OCH ₃	Br	H	OCH ₃	H	H
S	NHPR	H	NHPr	H	H	H	H
S	NHPr	H	NHPr	H	OCH ₃	H	H
S	H	NHPr	NHPr	H	H	H	H
S	H	NHPr	NHPr	H	OCH ₃	H	H
S	H	OCH ₃	NH ₂	H	OCH ₃	H	H
S	H	OCH ₃	NHPr	H	OCH ₃	H	H
SO ₂	H	OCH ₃	NHPr	H	OCH ₃	H	H
O	OCH ₃	H	Cl	H	OCH ₃	H	H
O	OCH ₃	H	Br	H	OCH ₃	H	H
O	NHPr	H	NHPr	H	H	H	H
SO ₂	H	OCH ₃	CN	H	OCH ₃	H	H
SO ₂	H	OCH ₃	NHCH ₂ CO ₂ R*	H	OCH ₃	H	H
SO ₂	H	OCH ₃	S-N-Bu	H	OCH ₃	H	H
SO ₂	H	OCH ₃	CH ₂ CO ₂ R*	H	OCH ₃	H	H
SO ₂	H	OCH ₃	SO ₂ CH ₃	H	OCH ₃	H	H
S	H	S-n-Bu	H	H	H	H	H
S	H	H	S-n-Bu	H	H	H	H

	Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
5	S	H	CH ₃	S-n-Bu	H	H	H	H
	S	H	OMe	Br	H	CF ₃	H	H
	S	H	OMe	Br	H	F	H	H
10	S	H	OMe	Br	H	Cl	H	H
	S	H	OMe	Br	H	Br	H	H
	S	H	OMe	Br	H	NMe ₂	H	H
15	S	H	OMe	Br	H	SMe	H	H
	S	H	OMe	Br	H	SO ₂ Me	H	H
20	S	H	OMe	Br	H	Ph	H	H
	S	H	H	H	Cl	OMe	H	H

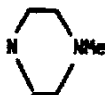
25 und R H oder C₂—C₄-Alkyl ist.
17. Verbindungen der Formel



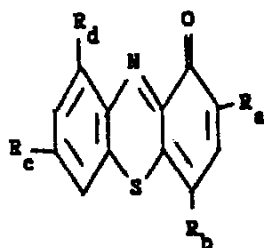
worin die Substituenten wie folgt sind:

	Y	R ₁	R ₂	R ₃	R ₄
40	S	H	H	S-n-CH ₄ H ₉	H
	S	OH	H	CH ₃	H
45	S	OCH ₃	H	CH ₃	H
	S	H	H	F	H
	S	H	H	CF ₃	H
50	S	H	H	Cl	CF ₃
	S	H	H	Cl	SCH ₃
55	S	H	H	Br	Cl
	S	H	H	CH ₃	Br
	S	H	H	F	Br
60	S	H	H	COCH ₃	Cl
	S	H	H	CF ₃	CH ₃
65	S	H	H	SC ₄ H ₉	CH ₃

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	Y	R ₁	R ₂	R ₃	R ₄
	S	H	H	CF ₃	Cl
5	S	H	H	Cl	CH ₂ COOR
	S	H	H	Cl	CH(Me)CO ₂ R
10	S	H	H	Cl	COCH ₃
	S	H	H	H	Cl
	S	H	H	H	Br
15	S	H	H	H	F
	S	H	H	H	CF ₃
20	S	H	H	H	CH ₃
	S	H	H	H	CH ₂ OH
	S	H	H	H	OCH ₃
25	S	H	H	H	SCH ₃
	S	H	H	H	COOR
30	S	H	H	H	CH ₂ CO ₂ R
	S	H	H	H	CH(Me)CO ₂ R
	SO ₂	H	H	NHPr	H
35	SO ₂	H	H		H
40	SO ₂	H	H	NH ₂	H
	SO ₂	H	H	NHPr	OCH ₃
	S	-1,4-dihydro-		H	H
45	S	H	H	NHPr	OCH ₃
	O	H	H	Cl	H
50	O	H	H	Br	H
	O	H	H	Br	OCH ₃
	O	H	H	NHPr	OCH ₃

55 und worin R H oder C₁—C₄-Alkyl ist.
18. Verbindungen der Formel



III

worin die Substituenten wie folgt sind:

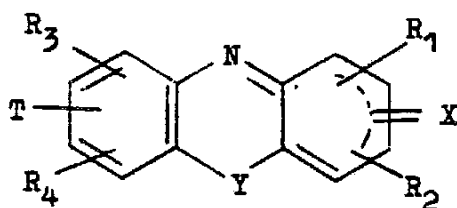
	R _a	R _b	R _c	R _d
5	t-Bu	t-Bu	H	H
	t-Bu	t-Bu	F	H
10	t-Bu	t-Bu	Me	H
	t-Bu	t-Bu	SMe	H
	t-Bu	t-Bu	H	OMe

19. Die Verbindung 2-S-Glutathionyl-3H-phenothiazin-3-on und 4-Chlor-2-S-glutathionylphenothiazin-3-on.

20. Die in Anspruch 1 beanspruchte Verwendung zur Herstellung eines Medikaments, die zusätzlich einen zweiten aktiven Bestandteil enthält, der ein nicht-steroides entzündungshemmendes Mittel ist; ein peripheres Analgetikum, ein Cyclooxygenaseinhibitor; ein Leukotrienantagonist; ein Antihistaminikum; ein Prostaglandinantagonist; oder ein Thromboxanantagonist, wobei das Gewichtsverhältnis der Verbindung der Formel I zum zweiten aktiven Bestandteil im Bereich von 10:1 bis 1:10 liegt.

Revendications

1. L'utilisation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'action des leucotriènes chez les mammifères, d'un composé de formule I, un composé qui est un sel d'un composé de formule I ou une composition pharmaceutique contenant un tel composé:



dans laquelle

X est dans la position 1 ou 3 et est O, S ou NR;

R est H, un alkyle ramifié ou linéaire en C₁₋₆, CN ou un phényle;

Y est O, Se, S, SO, SO₂ ou NR; et le pointillé représente une double liaison entre les positions 1 et 2 ou 2 et 3;

chacun de R₁, R₂, R₃ et R₄ indépendamment des autres est:

(1) un hydrogène,

(2) un alkyle en C₁₋₆,

(3) un alcényle en C₂₋₆,

(4) —(CH₂)_nM

où n est 0 ou un entier de 1 à 6 et M est

(a) OR₅,

(b) un halogène,

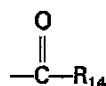
(c) CF₃,

(d) SR₅, où R₅ est H; un alkyle en C₁₋₆; un benzyle; un phényle ou un phényle substitué dont les substituants sont un alkyle en C₁₋₃, un halogène, CN, CF₃, COOR₆, CH₂COOR₆, (CH₂)_nNR₈R₉ où n est 0, 1 ou 2, un alcoxy en C₁₋₃, OH ou un halogénoalkyle en C₁₋₆; —(CH₂)_mCOOR₆, où m est 0 ou un entier de 1 à 6 et R₆ est H, un phényle ou un alkyle en C₁₋₆; CN, un formyle, CF₃ ou CH₂—R₁₂, où R₁₂ est un alkyle en C₁₋₅, un phényle ou un diméthylamino;

(e) un phényle ou un phényle substitué comme défini ci-dessus pour R₅;

(f) COOR₆;

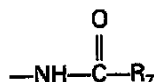
(g)



où R₁₄ est H, (CH₂)_nCOOR₆ où n est 0 ou un entier de 1 à 4, un alkyle en C₁₋₆, CF₃, un phényle ou un phényle substitué comme défini ci-dessus pour R₅;

(h) un tétrazole;

(i)



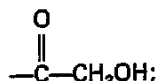
5 où R₇ est un alkyle en C₁₋₆, un benzyle ou un phényle;

(j) —NR₈R₉ où R₈ et R₉ sont indépendamment choisis parmi H, un phényle ou un phényle substitué comme défini ci-dessus pour R₅ ou un alkyle en C₁₋₄, un alkyl(C₁₋₄)aminoalkyle ou peuvent être unis par N pour former un radical 4-méthylpipérazinyle;

(k) —NHSO₂R₁₀ où R₁₀ est OH, un alkyle en C₁₋₆, un alcoxy en C₁₋₆, un phényle ou CF₃;

10

(l)



15 (m) —SOR₁₁ où R₁₁ est un alkyle en C₁₋₆, un phényle ou un phényle substitué comme défini ci-dessus pour R₅, (CH₂)_mCOOR₆ où m est 1 à 6, CN, un formyle ou CF₃;

(n) —CONR₈R₉;

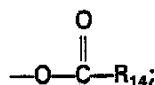
(o) —SO₂NR₈R₉;

(p) —SO₂R₁₃ où R₁₃ est OH, H, un alkyle en C₁₋₆, un phényle ou un phényle substitué comme défini ci-dessus pour R₅, (CH₂)_mCOOR₆ où m est 1 à 6, CN ou CF₃;

20

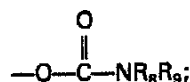
(q) NO₂;

(r)



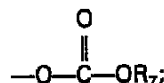
25

(s)



30

(t)



(u) —CN; ou

35 (v) NR₁₅R₁₆ où R₁₅ et R₁₆ sont chacun tels que HNR₁₅R₁₆ soit un amino-acide essentiel; ou deux quelconques de R₁, R₂, R₃ et R₄ sont unis pour former un quatrième cycle saturé ou insaturé en C₅₋₆; et

T est H, un halogène ou CF₃.

2. L'utilisation selon la revendication 1, dans laquelle, dans la formule I, X est en position 1.

40 3. L'utilisation selon la revendication 2, dans laquelle X est O ou NR.

4. L'utilisation selon la revendication 3, dans laquelle, dans la formule I, Y est S, SO, SO₂, NR ou O et dans l'unité structurale (CH₂)_nM, n est 0 ou 1.

5. L'utilisation selon la revendication 4, dans laquelle, dans la formule I, X est O et Y est S.

6. L'utilisation selon la revendication 1, dans laquelle, dans la formule I, X est en la position 3.

45 7. L'utilisation selon la revendication 6, dans laquelle X est O ou NR.

8. L'utilisation selon la revendication 7, dans laquelle, dans la formule I, Y est S, SO, SO₂, NR ou O et dans l'unité structurale (CH₂)_nM, n est 0 ou 1.

9. L'utilisation selon la revendication 8, dans laquelle Y est S ou O.

10. L'utilisation selon la revendication 9, dans laquelle X est O et Y est S.


50 11. L'utilisation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'action des leucotriènes chez les mammifères, d'un composé de formule I, un composé qui est un sel d'un composé de formule I ou une composition pharmaceutique contenant un tel composé, dans laquelle, dans la formule I, les variables sont comme défini ci-après, X étant en position 1:

55


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65

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Y	X	R ₁	R ₂	R ₃	R ₄	T
O	O	2-t-Bu	8-t-Bu	4-t-Bu	6-t-Bu	H
O	O	2-t-Bu	H	4-Me	H	H
S	S	2-t-Bu	4-t-Bu	H	H	H
N-CH ₃ , S, O, Se, SO ou SO ₂	O	2-Cl	H	H	H	H
"	O	2-SCF ₃	H	H	H	
"	O	2-S 	H	H	H	H
S	O	2-t-Bu	4-t-Bu	H	H	H
N-CH ₃ , S, O, Se, SO ou SO ₂	O	2-CN	H	H	H	H
"	O	H	3-CO ₂ Et	H	H	H
"	O	H	3-Cl	H	H	H
"	O	H	H	4-Cl	H	H
"	O	H	H	4-SO ₂ CH ₃	H	H
"	O	2-Cl	H	4-Cl	H	H
"	NH	2-Cl	H	4-Cl	H	H
"	NH	H	H	H	H	H
N-CN	O	2-Cl	H	4-Cl	H	H
S	O	H	H	H	H	H
S	O	2-Cl	3-Cl	4-Cl	7-Cl	9-Cl
S	O	2-Br	3-Br	4-Br	7-Br	9-Br
S	O	H	H	H	7-SO ₂ CH ₃	H
S	O	2-Cl	H	4-SO ₂ CH ₃	H	H
S	O	2-F	H	4-Cl	H	H
S	O	2-Br	H	H	H	H
S	O	2-CF ₃	H	H	H	H
S	O	2-SCF ₃	H	H	H	H
S	O	2-SO ₂ CF ₃	H	H	H	H
S	O	H	3-Cl	H	H	H
S	O	H	3-CO ₂ Et	H	H	H
S	O	H	3-CO ₂ H	H	H	H

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Y	X	R ₁	R ₂	R ₃	R ₄	T
S	O	H	3-CN	H	H	H
S	O	H	3-SCF ₃	H	H	H
S	O	H	H	4-Cl	H	H
S	O	H	H	4-SCF ₃	H	H
S	O	H	H	4-Cl	H	H
S	O	2-Br	H	4-Br	H	H
S	O	2-Cl	H	H	8-CN	H
S	O	2-Cl	H	H	8-CO ₂ Et	H
S	O	2-Cl	H	H	8-CO ₂ H	H
S	O	2-Cl	H	H	8-CF ₃	H
S	O	2-Cl	H	H	7-SO ₂ CH ₃	H
S	O	H	3-CONMe ₂	H	H	H
S	O	2-Cl	H	H	7-OCH ₃	H
S	O		H	H	H	H
S	O	2-SO ₂ CH ₃	H	H	H	H
S	O	2-CH ₂ CH=CH ₂	H	4-CH ₂ CH=CH ₂	H	H
S	O	H	3-N(CH ₃) ₂	H	H	H
S	O	H	H	4-Cl	7-S-C ₆ H ₅	H
S	O	2-CHCO ₂	H	H	H	H
S	O	2-Cl	H	4-SCH ₂ CO ₂ H	H	H
S	O	2-COC ₃	H	H	7-OCH ₃	H
S	O	H	H	4-CO-C ₆ H ₅	7-OCH ₃	H
S	NH	2-Cl	H	4-Cl	H	H
S	NH	H	3-N(CH ₃) ₂	H	H	H
S	NH	2-SCH ₃	H	4-SCH ₃	H	H
S	O	H	H	H	H	H
S	NH	H	H	H	H	H
S	O	2-COCH ₃	H	H	7-OCH ₃	H
S	O	H	H	4-COC ₆ H ₅	7-OCH ₃	H
S	NH.HCl	H	H	H	H	H
S	O	H	H	H	H	H

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Y	X	R ₁	R ₂	R ₃	R ₄	T
O	O	H	H	H	H	H
O	NH	H	H	H	H	H
O	S	H	H	H	H	H
O	NH.HCl	H	H	H	H	H
Se	O	H	H	H	H	H
Se	NH	H	H	H	H	H
Se	S	H	H	H	H	H
NH	NH.HCl	H	H	H	H	H
NH	S	H	H	H	H	H
O	O	4-Cl	H	H	H	H
O	O	4-Cl	H	7-OMe	H	H
O	O	4-Me	H	H	H	H
O	O	H	2-Cl	H	H	H
O	O	4-Cl	2-S-pPAA*	H	H	H
Se	O	4-Cl	H	H	H	H
Se	O	4-Cl	H	7-OMe	H	H
Se	O	4-Me	H	H	H	H
Se	O	4-Cl	2-S-pPAA*	H	H	H
N—CH ₃	O	4-Cl	H	H	H	H
N—C ₆ H ₅	O	4-Cl	H	7-OMe	H	H
N—H	O	4-Cl	2-S-pPAA*	H	H	H
S	O	4-Cl	H	H	H	H
SO	O	H	H	H	H	H
SO ₂	O	H	H	H	H	H
SO ₂	O	4-Cl	H	H	H	H
N—Me	O	H	H	H	H	H
N—Me	O	4-Cl	H	H	H	H
N—Me	O	4-Cl	H	7-OMe	H	H
NCN	O	4-Cl	H	H	H	H
NH	O	4-Cl	H	H	H	H
NH	O	4-Cl	H	H	H	H

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	Y	X	R ₁	R ₂	R ₃	R ₄	T
	S	O	2-t-Bu	9-t-Bu	4-OMe	H	H
5	S	O	2-t-Bu	7-t-Bu	4-F	H	H
	S	O	2-t-Bu	7-t-Bu	4-Me	H	H
10	S	O	2-t-Bu	7-t-Bu	4-SMe	H	H

*pPAA = acide paraphénylacétique.

12. L'utilisation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'action
 15 des leucotriènes chez les mammifères, d'un composé de formule I, un composé qui est un sel d'un
 composé de formule I ou une composition pharmaceutique contenant un tel composé, dans laquelle, dans
 la formule I, les variables sont comme défini ci-après, X étant en position 3:

	R ₁	R ₂	R ₃	R ₄	T
20	H	H	H	H	H
	2-Cl	H	H	H	H
25	H	H	6-Cl	H	H
	H	H	7-Cl	H	H
	H	H	8-Cl	H	H
30	H	H	9-Cl	H	H
	1-Cl	H	H	H	H
35	1-Cl	4-Cl	H	H	H
	2-Cl	4-Cl	H	H	1-Cl
	2-N(Me) ₂	H	H	H	H
40	2-SMe	H	H	H	H
	2-S-pPAA	H	H	H	H
45	2-C(O)CH ₃	H	H	H	H
	2-OMe	H	H	H	H
	H	H	H	7-CH ₂ CO ₂ H	H
50	H	H	H	8-CH ₂ COOH	H
	H	2-SO ₃ H	H	H	H
55	2-N(Me) ₂	H	H	H	H
	2-SMe	H	H	H	H
	2-C(O)CH ₃	H	H	H	H
60	2-OMe	H	H	H	7-I
	2-CH ₂ CO ₂ H	H	H	H	H
65	2-CH(CH ₃)CO ₂ H	H	H	H	H

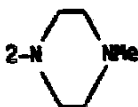
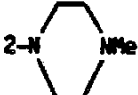
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R ₁	R ₂	R ₃	R ₄	T
4-CH ₂ COOH	H	H	H	H
4-CH(CH ₃)CO ₂ H	H	H	H	H
H	H	7-OH	6-propyl	H
4-Cl	H	H	H	H
4-F	H	H	H	H
4-F	H	7-Cl	H	H
4-Et	H	H	H	H
4-Et	H	7-OMe	H	H
4-Et	H	7-Cl	H	H
4-Cl	H	7-OMe	H	H
4-OMe	H	7-Cl	H	H
4-Cl	H	6-Cl	H	H
4-Cl	H	8-Cl	H	H
4-Cl	H	9-Cl	H	H
4-Cl	H	6-OMe	H	H
4-Cl	H	8-OMe	H	H
4-Cl	H	9-Et	H	H
4-Cl	H	6-Et	H	H
4-Cl	H	7-Et	H	H
4-Cl	H	8-Et	H	H
4-Cl	1-Et	H	H	H
4-Cl	2-Et	H	H	H
4-Cl	1-CH ₂ COOH	H	H	H
4-Cl	2-CH ₂ COOH	H	H	H
4-OH	2-OMe	7-OMe	H	H
4-OH	H	H	H	H
4-Me	1-OMe	2-OMe	H	H
4-Cl	H	6-CH ₂ COOH	H	H
4-Cl	H	7-CH ₂ COOH	H	H
4-Cl	H	8-CH ₂ COOH	H	H
4-Cl	2-N(Me) ₂	H	H	H


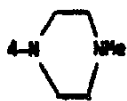

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R ₁	R ₂	R ₃	R ₄	T
4-Cl	1-N(Me) ₂	H	H	H
4-Cl	2-N(Me) ₂	7-OMe	H	H
4-Cl	2-N(Me) ₂	7-Cl	H	H
4-Cl	2-SMe	H	H	H
4-Cl	2-SCH ₂ COOH	H	H	H
4-Cl	2-S-pPAA	H	H	H
4-Cl	1-S-pPAA	H	H	H
4-Cl	2-S-pPAA	7-OMe	H	H
4-Cl	2-SO ₃ H	H	H	H
4-Cl	2-OMe	H	H	H
4-Cl	2-OMe	7-Cl	H	H
4-Cl	H	7F	H	H
4-OMe	H	7-OMe	H	H
4-OMe	H	7-Me	H	H
4-OMe	2-SMe	H	H	H
4-SMe	H	H	H	H
4-Br	H	H	H	H
4-I	H	H	H	H
4-Br	H	7-OMe	H	H
4-I	H	7-OMe	H	H
4-Br	2-Me	H	H	H
4-I	2-Me	H	H	H
4-Cl	H	7/8-(CH ₂) ₄ —		H
4-Cl	H	7/8-(CH ₂) ₃ —		H
4-Br	2-OMe	7-OMe	H	H
7-F	H	H	H	H
7-NH ₂	H	H	H	H
2-Me	7-N(Me) ₂	H	H	H
7-N(Me) ₂	H	H	H	H
1-CO ₂ H	4-OH	7-NMe ₂	H	H
1-Cl	2-Cl	4-Cl	H	7-Cl

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R ₁	R ₂	R ₃	R ₄	T
1-Me	7-Me	H	H	4-Cl
2-Me	7-Me	H	H	4-Cl
2-Me	H	H	H	4-Cl
7-Me	H	H	H	4-Cl
9-OMe	H	H	H	H
2-OMe	H	H	H	7-F
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	7-Me	H	H
1-Me	7-Me	H	H	H
2-Me	7-Me	H	H	H
2-Cl	4-Cl	H	H	7-F
1-Cl	4-Cl	H	H	7-F
2-OMe	7-SMe	H	H	H
H	H	H	H	4-CF ₃
2-CF ₃	H	H	H	4-CF ₃
4-COMe	H	H	H	H
2-OEt	H	H	H	4-Cl
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
9-OMe	H	H	H	H
2-OMe	H	H	H	H
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	4-Me	H	H
4-OMe	H	H	H	H
1-OMe	7-OMe	H	H	4-Br
1-OMe	7-OMe	2-Cl	H	4-Cl
1-OMe	7-OMe	H	H	4-Cl
	7-OMe	H	H	H
	7-OMe	H	H	4-Br

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R ₁	R ₂	R ₃	R ₄	T
2-OMe	4-OH	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
		H	H	H
4-COMe	H	H	H	H
2-NHPr	4-NHPr	H	H	H
2-OMe	4-CN	7-OMe	H	H
2-OMe		7-OMe	H	H
2-OMe	7-OMe	H	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-NHPr	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
2-NHPr	4-NHPr	7-OMe	H	H
2-OMe	4-NH ₂	7-OMe	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-OMe	4-Cl	7-OMe	H	H
1-OMe	4-Br	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-OMe	4-CN	7-OMe	H	H
2-OMe	4-NHCH ₂ CO ₂ R*	7-OMe	H	H
2-OMe	4-S-7-Bu	7-OMe	H	H
2-OMe	4-CH ₂ CO ₂ R*	7-OMe	H	H
2-OMe	4-SO ₂ Me	7-OMe	H	H
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
2-OMe	7-Me	H	H	4-Br
2-OMe	7-CF ₃	H	H	4-Br
2-OMe	7-F	H	H	4-Br
2-OMe	7-Cl	H	H	4-Br

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	R ₁	R ₂	R ₃	R ₄	T
5	2-OMe	7-Br	H	H	4-Br
	2-OMe	7-NMe ₂	H	H	4-Br
	2-OMe	7-SMe	H	H	4-Br
10	2-OMe	7-SO ₂ Me	H	H	4-Br
	2-OMe	7-Ph	H	H	4-Br
15	1-Me	H	H	H	4-Br
	2-Me	H	H	H	H
	2-OEt	H	H	H	H
20	7-Cl	H	H	H	H
	9-Cl	H	H	H	H
25	7-F	H	H	H	H
	7-Me	H	H	H	H
	7-OMe	H	H	H	H
30	2-Cl	H	H	H	4-Cl
	1-Me	7-Me	H	H	4-Cl
35	1-Me	7-Me	H	H	H
	2-OMe	7-OEt	H	H	H
	2-NH ₂	H	H	H	H
40	7-OH	H	H	H	H

*pPAA = acide paraphénylacétique.

et dans laquelle R est H ou un alkyle en C₁ à C₄.

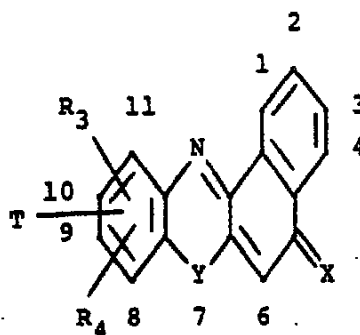
45 13. L'utilisation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'action des leucotriènes chez les mammifères, d'un composé de formule I, un composé qui est un sel d'un composé de formule I ou une composition pharmaceutique contenant un tel composé, dans laquelle, dans la formule I, les variables sont comme défini ci-après, X étant en position 3:

	Y	X	R ₁	R ₂	R ₃	R ₄	T
50	S	O	2-OMe	7-OMe	H	H	H
	S	O	1-OMe	7-OMe	H	H	H
55	S	O	2-OMe	7-OMe	H	H	1-Br
	S	O	1-OMe	7-OMe	H	H	2-Br
60	S	O	1-OMe	7-OMe	H	H	4-Br
	S	O	1-OMe	7-OMe	H	H	2-Cl
	S	O	1-OMe	7-OMe	H	H	4-Cl
65							

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	Y	X	R ₁	R ₂	R ₃	R ₄	T
	S	O	2-OMe	7-OMe	H	H	1-Cl
5	S	O	2-OMe	7-OMe	H	H	4-Cl
	S	O	2-OEt	7-OEt	H	H	1-Br
10	S	O	2-OEt	7-OEt	H	H	4-Br
	S	O	2-OEt	7-OEt	H	H	1-Cl
	S	O	2-OEt	7-OEt	H	H	4-Cl
15	S	O	2-OMe	7-OMe	8-OMe	H	1-Br
	S	O	2-OMe	7-OMe	8-OMe	H	4-Br
20	S	O	2-OMe	7-OMe	H	H	4-F
	S	O	2-OMe	7-OMe	H	H	4-CF ₃
	S	O	2-OMe	7-OEt	H	H	4-Be
25	S	O	2-OMe	7-OEt	H	H	4-Cl
	S	O	2-OMe	7-OEt	H	H	4-F
	S	O	2-OMe	7-OEt	H	H	4-CF ₃
30	S	O	2-OEt	7-OMe	H	H	4-Br
	S	O	2-OEt	7-OMe	H	H	4-Cl
35	S	O	2-OEt	7-OMe	H	H	4-F
	S	O	2-OEt	7-OMe	H	H	4-CF ₃
40	S	O	2-OMe	7-OMe	H	H	4-Br

14. L'utilisation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'action des leucotriènes chez les mammifères, d'un composé de formule I, un composé qui est un sel d'un composé de formule II:



dans laquelle les substituants sont:

	Y	X	R ₃	R ₄	T
60	O	O	H	H	H
	S	O	H	H	H
65	SO	O	H	H	H

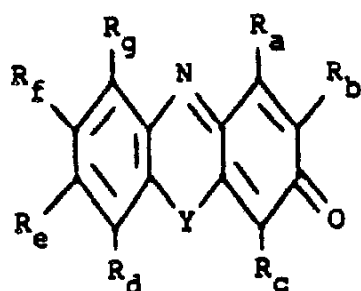
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Y	X	R ₃	R ₄	T
SO ₂	O	H	H	H
SO	O	H	H	6-Cl
S	O	6-COCH ₃	H	H
S	O	6-CH ₃	H	H
SO ₂	O	6-OH	H	H
SO ₂	O	6-OMe	H	H
S	O	9-OMe	H	H
S	O	6-OH	H	H
S	O	6-OMe	H	H
S	O	6-NHCOMe	H	H
S	O	6-NHPh	H	H
S	O	H	H	6-Br
S	O	6-NHMe	H	H
S	O	6-NH-t-Bu	H	H
S	O	6-NH-COMe	H	9-Cl
S	O	6-NH-COMe	9-Ome	H
S	O	6-NHPh-p-Br	H	9-Cl
O	O	H	H	6-Cl
O	O	H	H	6-Br
O	O	9-OMe	H	6-Br
O	O	9-OMe	6-NHPr	H
S	O	6-CF ₃	H	H
S	O	6-S-n-Bu	H	H
S	O	6-OMe	H	9-Cl
S	O	9-OMe	H	6-Cl
S	O	6-OMe	9-OMe	H
S	O	6-Cl	9-Me	11-Br
S	O	6-NHPh	9-Me	11-Br
S	O	6-Me	H	H
O	NH	9-NMe ₂	10-Me	H
O	NH	9-N(Et) ₂	H	H
S	O	6-Cl	H	H

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15. L'utilisation selon l'une quelconque des revendications 1 à 14, appliquée au traitement de (1) les affections pulmonaires, (2) l'inflammation, (3) les allergies, (4) la douleur, (5) les affections cardiovasculaires ou (6) les affections cutanées.

16. Les composés de formule:



dans laquelle les substituants sont:

20	Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
	S	H	SCH ₃	H	H	H	H	H
	S	H	H	SCF ₃	H	H	H	H
25	S	H	H	CHO	H	H	H	H
	S	H	H	COCF ₃	H	H	H	H
30	S	H	H	H	H	SCH ₃	H	H
	S	H	H	H	H	CO ₂ CH ₃	H	H
	S	H	H	H	H	CO ₂ H	H	H
35	S	H	H	H	H	CHO	H	H
	S	H	H	H	H	CONH ₂	H	H
40	S	H	H	H	H	CH ₂ OH	H	H
	S	H	H	Cl	H	CO ₂ Me	H	H
	S	H	H	Cl	H	CO ₂ H	H	H
45	S	H	H	Cl	H	CHO	H	H
	S	H	H	Cl	H	CONH ₂	H	H
50	S	H	H	Cl	H	CH ₂ OH	H	H
	S	H	O-benzyl	Cl	H	H	H	H
	S	H	OEt	H	H	CH ₃	H	H
55	S	CH ₃	H	Cl	H	CH ₃	H	H
	S	H	CH ₃	Cl	H	CH ₃	H	H
60	S	H	OMe	Br	H	OMe	H	H
	S	H	OMe	Cl	H	OMe	H	H
	S	H	OEt	Br	H	OEt	H	H

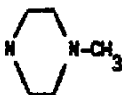
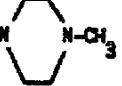
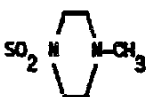

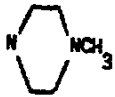
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Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
S	H	OMe	Br	H	Me	H	H
S	H	H	CHO	H	H	H	H
S	H	H	COCF ₃	H	H	H	H
S	H	H	H	H	SCH ₃	H	H
S	H	H	H	H	OCH ₃	H	H
S	H	H	H	H	CO ₂ CH ₃	H	H
S	H	H	H	H	CO ₂ H	H	H
S	H	H	H	H	CN	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	CONH ₂	H	H
S	H	H	H	H	CH ₂ OH	H	H
S	H	H	H	H	CF ₃	H	H
S	CH ₃	H	Cl	H	H	H	H
S	H	CH ₃	Cl	H	H	H	H
S	H	H	Cl	H	F	H	H
S	H	Cl	Cl	H	F	H	H
S	H	CH ₃	H	H	F	H	H
S	CH ₃	H	H	H	F	H	H
S	H	H	Cl	H	OMe	H	H
S	H	H	Cl	H	CF ₃	H	H
S	H	H	Cl	H	CO ₂ Me	H	H
S	H	H	Cl	H	CO ₂ H	H	H
S	H	H	Cl	H	CN	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	CONH ₂	H	H

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Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
S	H	H	Cl	H	CH ₂ OH	H	H
S	H	H	OCH ₃	H	Cl	H	H
S	H	H	CF ₃	H	Cl	H	H
S	H	OEt	Cl	H	H	H	H
S	H	OiPr	H	H	H	H	H
S	OMe	H	Cl	H	H	H	H
S	OEt	H	Cl	H	H	H	H
S	H	OiPr	Cl	H	H	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	F	H	H
S	H	OCH ₃	Cl	H	H	H	H
S	H	OEt	H	H	CH ₃	H	H
S	H	OEt	Cl	H	F	H	H
S	H	OEt	Cl	H	CH ₃	H	H
S	H	H	Cl	H	CH ₃	H	H
S	H	CH ₃	Cl	H	H	H	H
S	H	CH ₃	Br	H	H	H	H
S	CH ₃	H	H	H	CH ₃	H	H
S	H	CH ₃	H	H	CH ₃	H	H
S	CH ₃	H	Cl	H	CH ₃	H	H
S	H	CH ₃	Cl	H	CH ₃	H	H
S	Cl	H	Cl	H	F	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
O	H	H	Cl	H	H	H	H
S	H	OMe	Br	H	Me	H	H

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Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
SO ₂	H	H	OH	H	H	H	H
SO ₂	H	OMe	OH	H	OMe	H	H
SO ₂	OMe	OMe	Me	H	H	H	H
SO ₂	H	H	OMe	H	H	H	H
SO ₂	H	OMe	OMe	H	OMe	H	H
S	H	H	H	H	H	H	OCH ₃
S	H	OCH ₃	H	H	F	H	H
S	H	OCH ₃ H	OCH ₃	H	H	H	H
S	OCH ₃	OCH ₃	Me	H	H	H	H
S	H	H	COCH ₃	H	H	H	H
S	OCH ₃	H	Br	H	OCH ₃	H	H
S	OCH ₃	Cl	Cl	H	OCH ₃	H	H
S	OCH ₃	H	Cl	H	OCH ₃ H	H	H
S	H		H	H	OCH ₃	H	H
S	H		Br	H	OCH ₃	H	H
SO ₂	H	OCH ₃	OH	H	OCH ₃	H	H
SO ₂	NHPr	H	NHPr	H	H	H	H
SO ₂		H		H	H	H	H
SO ₂	H	OCH ₃		H	OCH ₃	H	H
SO ₂	H	OCH ₃	Br	H	OCH ₃	H	H
S	NHPr	H	NHPr	H	H	H	H
S	NHPr	H	NHPr	H	OCH ₃	H	H
S	H	NHPr	NHPr	H	H	H	H
S	H	NHPr	NHPr	H	OCH ₃	H	H
S	H	OCH ₃	NH ₂	H	OCH ₃	H	H
S	H	OCH ₃	NHPr	H	OCH ₃	H	H
SO ₂	H	OCH ₃	NHPr	H	OCH ₃	H	H
O	OCH ₃	H	Cl	H	OCH ₃	H	H

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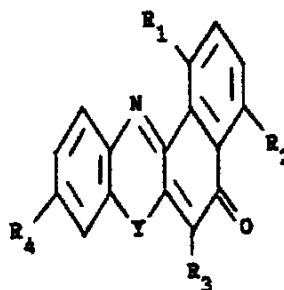
	Y	R _a	R _b	R _c	R _d	R _e	R _f	R _g
	O	OCH ₃	H	Br	H	OCH ₃	H	H
5	O	NHPr	H	NHPr	H	H	H	H
	SO ₂	H	OCH ₃	CN	H	OCH ₃	H	H
10	SO ₂	H	OCH ₃	NHCH ₂ CO ₂ R*	H	OCH ₃	H	H
	SO ₂	H	OCH ₃	S-n-Bu	H	OCH ₃	H	H
	SO ₂	H	OCH ₃	CH ₂ CO ₂ R*	H	OCH ₃	H	H
15	SO ₂	H	OCH ₃	SO ₂ CH ₃	H	OCH ₃	H	H
	S	H	S-n-Bu	H	H	H	H	H
20	S	H	H	S-n-Bu	H	H	H	H
	S	H	CH ₃	S-n-Bu	H	H	H	H
	S	H	OMe	Br	H	CF ₃	H	H
25	S	H	OMe	Br	H	F	H	H
	S	H	OMe	Br	H	Cl	H	H
30	S	H	OMe	Br	H	Br	H	H
	S	H	OMe	Br	H	NMe ₂	H	H
	S	H	OMe	Br	H	SMe	H	H
35	S	H	OMe	Br	H	SO ₂ Me	H	H
	S	H	OMe	Br	H	Ph	H	H
40	S	H	H	H	Cl	OMe	H	H

et R est H ou un alkyle en C₂ à C₄.

17. Les composés de formule:

45


50



55 dans laquelle les substituants sont:

	Y	R ₁	R ₂	R ₃	R ₄
	S	H	H	S-n-CH ₄ H ₉	H
60	S	OH	H	CH ₃	H
	S	OCH ₃	H	CH ₃	H
65	S	H	H	F	H

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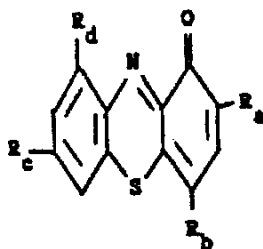
Y	R ₁	R ₂	R ₃	R ₄
S	H	H	CF ₃	H
S	H	H	Cl	CF ₃
S	H	H	Cl	SCH ₃
S	H	H	Br	Cl
S	H	H	CH ₃	Br
S	H	H	F	Br
S	H	H	COCH ₃	Cl
S	H	H	CF ₃	CH ₃
S	H	H	SC ₄ H ₉	CH ₃
S	H	H	CF ₃	Cl
S	H	H	Cl	CH ₂ COOR
S	H	H	Cl	CH(Me)CO ₂ R
S	H	H	Cl	COCH ₃
S	H	H	H	Cl
S	H	H	H	Br
S	H	H	H	F
S	H	H	H	CF ₃
S	H	H	H	CH ₃
S	H	H	H	CH ₂ OH
S	H	H	H	OCH ₃
S	H	H	H	SCH ₃
S	H	H	H	COOR
S	H	H	H	CH ₂ CO ₂ R
S	H	H	H	CH(Me)CO ₂ R
SO ₂	H	H	NHPr	H
SO ₂	H	H		H
SO ₂	H	H	NH ₂	H
SO ₂	H	H	NHPr	OCH ₃
S	-1,4-dihydro-		H	H
S	H	H	NHPr	OCH ₃
O	H	H	Cl	H

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Y	R ₁	R ₂	R ₃	R ₄
O	H	H	Br	H
O	H	H	Br	OCH ₃
O	H	H	NHPr	OCH ₃

10 et dans laquelle R est H ou un alkyle en C₁ à C₄.

18. Les composés de formule:



III

dans laquelle les substituants sont:

R _a	R _b	R _c	R _d
t-Bu	t-Bu	H	H
t-Bu	t-Bu	F	H
t-Bu	t-Bu	Me	H
t-Bu	t-Bu	SMe	H
t-Bu	t-Bu	H	OMe

19. Les composés 2-S-glutathionyl-3H-phénothiazine-3-one et 4-chloro-2-S-glutathionylphénothiazine-3-one.

20. L'utilisation, selon la revendication 1, pour la fabrication d'un médicament qui contient de plus un second ingrédient actif qui est un agent anti-inflammatoire non stéroïdien; un agent analgésique périphérique; un inhibiteur de la cyclooxygénase; un antagoniste des leucotriènes; un agent antihistaminique; un antagoniste des prostaglandines; ou un antagoniste du thromboxane, dans lequel le rapport pondéral du composé de formule I au second ingrédient actif est dans la gamme de 10/1 à 1/10.